STRESS ECHOCARDIOGRAPHY IN THE EVALUATION OF CORONARY ARTERY DISEASE

(Stress echocardiografie voor de evaluatie van coronairlijden)

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CONTENTS

To my mother

GENERAL OVERVIEW

Coronary flow reserve is the capability of the coronary artery to dilate in response to myocardial metabolic requirements (1). It exhausts itself when the vasodilatation is extreme: this means, in a normal subject, a four-fold increase in the resting flow.

Myocardial ischemia results from a supply-demand imbalance between coronary blood flow and myocardial metabolic requirements.

The commonest mechanism of ischemia is due to a reduced subendocardial coronary blood flow secondary to a fixed stenosis: the severity of stenosis determines the clinical scenarios (2). An advanced degree of coronary arterial obstruction may exist without signs of myocardial ischemia or underperfusion at rest (3). Ischemia can be induced by stenoses of lesser severity if they prevent the development of coronary hyperemia in response to increased oxygen demand (4).

Myocardial ischemia in a single territory is associated with three clinical manifestations: abnormal regional left ventricular function, ECG changes, and chest pain (5-7).

The sequence of functional events induced by ischemia begins with diminished left ventricular diastolic compliance followed by decreased myocardial contractility and increased left ventricular end-diastolic pressure.

The correlation between myocardial flow and contractility is well know. In 1935 Tennant and Wiggers showed in a dog that occlusion for several minutes of a proximal LAD resulted in a reduction of regional myocardial contraction (8). Deprivation of the myocardium of oxygen rapidly leads to a depression of its contractile function.

The various stress tests to detect or assess coronary artery disease reproduce the imbalance between myocardial demand and supply which precipitate ischemia. (9).

Provocative stress tests can be divided into two groups according to their pathophysyological mechanism of ischemia:

- stress modalities that primarily increase myocardial oxygen demand by increasing heart rate and contractility such as physical exercise, atrial pacing and inotropic agents. These include dobutamine and arbutamine (10-17).

- stress modalities that primarily reduce myocardial oxygen supply by inducing or enhance maldistribution of myocardial blood flow. These include pharmacologic coronary vasodilators such as dipyridamole and adenosine (18-20).

Echocardiographic techniques used with physical exercise or in conjunction with pharmacological agents, have been shown to provide information regarding the presence, severity and distribution of coronary artery disease with a comparable accuracy to others techniques (21-24).

Exercise echocardiography has several advantages: it represents the most physiological stress to the cardiocirculatory system, it gives information about exercise capacity and the ischemic threshold can be estimated. However it is technically demanding because adequate images are difficult to record during exercise and hyperventilation-induced artefacts are rather common Post-exercise recording of the echocardiographic images has been reported but results in false negative studies due to rapid resolution of ischemia. These factors decrease the sensitivity of the method.

Pharmacological stress overcomes most of these disadvantages. The test can be performed in patients unable to exercise. Dobutamine and dipyridamole are the most commonly used pharmacologic agents in conjunction with echocardiography in the diagnosis and prognosis of patients with coronary artery disease.

Background of dobutamine-atropine stress echocardiography

Dobutamine is a synthetic sympathicomimetic amine which stimulates ß1, ß2 and a1 receptors and is currently used for the short-term treatment of patients with heart failure due to its positive inotropic and chronotropic effect (15). Dobutamine increases myocardial oxygen demand through a positive chronotropic and inotropic effect on the heart (25) and is therefore regarded as an exercise-simulating agent.

The marked inotropic effect is mediated by both a1 and ß1 receptor stimulation, while ß1 stimulation is responsible for its chronotropic effect. Dobutamine causes an increase in cardiac output, due to an increase in stroke volume and a decrease in systemic vascular resistance due to a secondary reflex withdrawal of sympathetic tone. In the peripheral vasculature the a1 mediated vasoconstriction is balanced by the ß2 mediated vasodilation. Consequently, systemic blood pressure usually remains unaffected during dobutamine infusion or may moderately increase.

Low-dose dobutamine (up to 10 µg/kg/min) infusion causes a nearly maximum positive inotropic effect without a significant increase in heart rate. This may improve the contractile function of hibernating or stunned myocardium and allow its detection. The increase in myocardial oxygen consumption during high dose dobutamine infusion (up to 40 µg/kg/min), closely resembles physical exercise (15), is related to its chronotropic (26) rather than its inotropic

response. Besides an increase in myocardial oxygen demand, dobutamine may also induce a maldistribution of coronary blood flow due its coronary vasodilator effect with an endo-epicardial maldistribution further potentiating the ischemia effect (27). In patients who fail to reach the test end-point (target heart rate or signs or symptoms of ischemia) with maximal dobutamine dose, atropine (28) may be added to "boost" the heart rate by its vagolytic action thus potentiating the positive chronotropic effect of dobutamine. Starting dose is 0.25 mg i.v. up to a maximum of 1.0 mg.

Echocardiography: The signs and symptoms of myocardial ischemia follow a "cascade" of events, starting with perfusion heterogeneity between subendocardial and subepicardial regions, metabolic changes, disturbance of ventricular relaxation, decrease in contractile function and late appearance of electrocardiographic changes and chest pain (29). Echocardiography allows to detect ischemia induced wall motion abnormalities which occur at an early stage of this sequence: reduced wall thickening and transient regional wall motion abnormalities. These are divided into three degrees of severity: hypokinesis (reduction of systolic movement), akinesis (absence of systolic movement), and dyskinesis (paradoxical systolic movement). The normal myocardium shows an increase of normal movement and thickening during dobutamine infusion.

Image analysis: In areas with a normal resting echocardiographic wall motion some investigators use absence of wall thickening as an early sign of ischemia, but is rather difficult to assess. This may be classified as "relative" hypokinesia (30). Other investigators use the combination of reduced wall thickening and wall motion as a more definite marker. In practice wall motion and wall thickening abnormalities always occur simultaneously, with a few exceptions as seen in the interventricular septum after cardiac surgery. Wall motion score is determined at rest and during stress using a semi-quantitative assessment. The left ventricular wall is divided into 16 segments (31) and each is scored using a 4-point scale: 1= normal, 2= hypokinetic (decrease of movement and systolic thickening), 3= akinetic (absence of movement and systolic thickening), and 4= dyskinetic (paradoxical outward movement).

The interpretation of wall motion changes in areas with resting abnormalities is more difficult but any deterioration of wall motion is considered abnormal. However, an akinetic segment at rest which does not improve during low-dose dobutamine stimulation but becomes dyskinetic at peak stress should be considered as a mechanical phenomenon compatible with scar tissue (32).

Pharmacological stress echocardiography has been shown to have good reproducibility (33,34) and to provide a useful tool for assessing

disease progression and the effects of therapeutic drugs in patients with coronary artery disease.

Interpretation of dobutamine stress testing is subjective. Despite this, the inter- and intra-observer variability in different studies have been reported to be good (35), but the inter-observer variability is relative low among different centers. In a recent study Hoffmann shows that the heterogeneity in data acquisition and assessment criteria among different centers results in low interinstitutional agreement in interpretation of stress echocardiography. Agreement is higher in patients with no or advanced coronary artery disease and substantially lower in those with limited echocardiography image quality. To increase agreement, he suggested a better standardization of image acquisition and reading criteria of stress echocardiography (36).

The diagnostic accuracy of stress echocardiography depends on the "expertise" of the investigator and there is definitely a "learning curve". Training is necessary and Picano et al (37) suggest that 100 stress echocardiographic studies should be analysed under expert supervision.

Dobutamine infusion protocol: at the Thoraxcentrecenter a "standard" dobutamine stress protocol has been developed which is now increasingly being used by others (28). This protocol allows patients to continue their anti-anginal medication, especially beta blocking agents which may diminish the action of dobutamine. This effect can be counteracted by the addition of atropine in patients who do not reach the target heart rate at maximal dose dobutamine infusion. The safety of the addition of atropine has been demonstrated (38).

Patients undergo a precordial two-dimensional echocardiographic examination at rest. A 12-lead ECG and standard apical and parasternal views are recorded on video tape and stored on an optical disk . Dobutamine is then administrated intravenously by infusion pump. "Low-dose" dobutamine echocardiography has been proposed for the evaluation of myocardial viability. Low-dose protocol starts at 5 µg/kg/minute for 3 minutes up to 10 µg/kg/minute for 3 minutes.

High dose dobutamine starts at 10 µg/kg/minute for 3 minutes, increasing by 10 µg/kg/minute every 3 minutes to a maximum of 40 µg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age predicted maximal heart rate who had no symptoms or signs of ischemia, atropine starting with 0.25 mg increasing to a maximum of 1 mg is given intravenously at the end of stage 4, while dobutamine infusion is continued. Throughout dobutamine infusion the ECG is continuously monitored, the 12-lead ECG is recorded each minute and the blood pressure is measured by sphygmomanometer or an automatic device every 3 minutes. The cross sectional echocardiogram is monitored and digitally recorded and dis-

played on quad screen for side by side comparison at the end of every stage. The stress images are also recorded on video tape during the final minute of each stage. Metoprolol (1 to 5 mg IV) is used to reverse the effect of dobutamine or dobutamine-atropine combination if this does not occur spontaneously and quickly. Atropine is used if bradycardia and hypotension occur. Off-line assessment of echographic images is usually independently performed by two investigators. In case of disagreement, a third investigator reviews the images and a majority decision is achieved.

Test end-point of dobutamine-atropine stress test: test end-point is a target of 85% of maximal heart rate (male: 220-age[years] X 85%; female: 200-age[years] X 85%). Interruption criteria for the test are: a new wall motion abnormality, horizontal or downsloping ST segment depression >2 mm at 80 ms after the J point, ST segment elevation, significant chest pain, reduction in systolic blood pressure >40 mmHg from that at rest, hypertension (systolic blood pressure > 220 mmHg), decrease of heart rate >10 beats per minute from that at rest, or any other side effect regarded as being due to dobutamine.

Dobutamine stress testing is feasible and safe (38). Poldermans showed that during 652 examinations the test was not completed in 16 patients despite absence of signs or markers of ischemia for limiting adverse effects, yielding an overall feasibility of 98%. These results are comparable with dipyridamole echocardiography (39), which showed a feasibility of 99%. Adverse effects consisted mostly of hypotension and cardiac arrhythmia's (40,44). As shown by Marwick (45) and Salustri (46) in their studies about 30% of patients developed significant dose-limiting side-effects. The frequency and severity of side-effects varies between studies; if all side-effects are included they may be recorded in up to 82% of patients (47), while a frequency of only 5% has been reported if only serious, dose-limiting side-effects are considered (48).

During the last few years many clinical studies have been performed at the Thoraxcenter of the Erasmus University Rotterdam, addressing the role of stress echocardiography in different clinical scenarios.

The studies present in this thesis were designed to further explore the clinical value of dobutamine and exercise stress echocardiography in patients with suspected or proven coronary artery disease and compare it with nuclear imaging.

The specific aims and topics of the studies were the following:

Chapter 1

Digital acquisition and display of echocardiographic images is mandatory particularly when exercise stress is used. In this chapter the principles of digital stress echocardiography are described.

Chapter 2

The safety and feasibility of any new stress test is a major issue before it can be implemented in clinical practice. In this chapter the safety and the feasibility of high dose dobutamine-atropine stress echocardiography has been studied in a large series of consecutive patients.

In particularly, the incidence and clinical significance of hypotension and tachyarrhythmias have been studied.

Chapter 3

The interpretation of stress echocardiography is semi-quantitative. Although the inter- and intra-observer variability of the interpretation in some centers have been reported to be good, no study has reported the inter-observer variability of stress echocardiography results among observers belonging to different centers. In this chapter the inter-observer variability of the results from five centers with a well-established experience of stress echocardiography is reported.

Chapter 4

Although many studies using stress echocardiography have been published, only sparse data are available on the relationship between exercise echocardiography and quantitative coronary arteriography. In this study a group of patients with no previous myocardial infarction and a moderate to severe stenosis of one coronary artery, underwent both exercise echocardiography (bicycle ergometry, post-exercise echocardiography) and coronary arteriography with quantitative analysis. The study aimed to assess which angiographic parameter and which cut-off of each angiographic parameters was the best predictor of an ischemic response on the echocardiography.

Chapter 5

This study has a similar design to that presented in Chapter 5, but included a homogeneous group of patients with proximal left anterior descending artery disease. To obtain additional information on myocardial perfusion MIBI SPECT was performed simultaneously with exercise echocardiography.

Chapter 6

Dobutamine-atropine stress echocardiography was compared to quantitative coronary arteriography in a consecutive group of patients without previous myocardial infarction and single vessel coronary artery disease. Similarly to chapters 4 and 5, the specific aim of the study was to investigate which is the best quantitative angiographic descriptor of an ischemic response during high dose dobutamine-atropine echocardiography.

Chapter 7

The presence of a left bundle branch block has always represented the "Achilles' heel" of noninvasive imaging methods in the diagnosis of coronary artery disease. In particular, stress-redistribution perfusion scintigraphy has a high sensitivity but a low specificity.

The aim of the study which was undertaken in cooperation with the University of Brussels (B), was to test the hypothesis that, using dobutamine stress, the mechanical marker of ischemia (a new wall motion abnormality) has a better diagnostic accuracy when compared with scintigraphic markers (transient perfusion abnormalities) for the diagnosis of coronary artery disease.

Chapter 8

The assessment of myocardial ischemia in regions with abnormal wall motion in a resting condition, and in particular the akinetic regions is problematic. In this chapter we have studied akinetic segments becoming dyskinetic during high dose dobutamine-atropine stress testing. The study was designed to test the hypothesis that akinetic regions becoming dyskinetic at peak dobutamine stress without improvement of wall thickening during low dose dobutamine are consistent with the presence of infarcted myocardium without ischemic areas which could be considered for revascularization. Perfusion scintigraphy simultaneously performed with echocardiography as a reference for the characterization of the absence of ischemia.

Chapter 9

Nuclear methods have recently are considered as the best approach to demonstrate myocardial viability.

However the merit of the newest technetium 99m labeled radiotracers, like Tc 99m MIBI, compared to the more established thallium 201 and PET tracers (FDG, ammonia), remains controversial. Also the concordance between stress echocardiography and MIBI SPECT for the assessment of myocardial viability has not been validated.

This chapter we report data of a study in which we analyzed the agreement between MIBI-SPECT, thallium and low-dose dobutamine echocardiography to detect myocardial viability.

Chapter 10

The pre-operative prediction of improvement of left ventricular dysfunction after coronary revascularization is clinically important.

We compared the low-dose dobutamine echocardiography and of thallium scintigraphy to identify viable myocardium in a group of patients with severe chronic left ventricular dysfunction prior to successful surgical coronary revascularization. In particular, we

compared the relative role of low-dose dobutamine echocardiography with thallium SPECT to predict the improvement of regional wall motion three months after revascularization.

Chapter 11

The pre-operative identification of patients at increased risk of peri-operative cardiovascular complications undergoing a major noncardiac vascular surgery is an important clinical issue. On average 10% of these patients have a cardiac complication, even in the absence of a history of coronary artery disease. They are mostly old and unable to perform an exercise test which prevents an adequate cardiovascular evaluation. Dipyridamole thallium scintigraphy has been shown to be useful in this clinical setting, but the specificity of this approach to identification of patients at risk is still too low. In a previous study at our center we have shown that dobutamine stress echocardiography is an alternative useful method for the identification of low risk patients. However this study was relatively small and the analysis of the stress echocardiography results was highly simplified, since the outcome of the test was limited to a binary classification of the test as positive or negative. Accordingly, in the present study we doubled the size of the patient group and we analyzed in more detail the stress echocardiography results, considering the extent, the severity and the threshold of ischemia as well. Our purpose was to identify a group at risk as small as possible, improving the specificity and, possibly, the cost-effectiveness of the test, if it will be used for screening in future risk reduction trials.

Chapter 12

The data in this study represent an extension of those in chapter 11. All patients who survived vascular surgery were followed-up for an average period of 19 months. The specific aims of this study were: 1) to describe the incidence of the overall long term cardiac and noncardiac mortality and morbidity in this population; 2) to assess the value of clinical and stress echocardiographic results performed before surgery to predict the late occurrence of cardiac mortality and morbidity.

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CHAPTER I

DIGITAL STRESS ECHOCARDIOGRAPHY*

During the last few years stress echocardiography has grown to become an established technique for assessing patients with proven or suspected coronary disease (1,2).

Several stress modalities have been applied to stress echocardiography, including physical exercise, atrial pacing and pharmacological methods, like dipyridamole, adenosine and dobutamine (1-3).

The aim of stress echocardiography is to detect a mechanical marker of myocardial ischaemia, which is the worsening of wall thickening at peak stress. More recently, it has been demostrated that stress echocardiography is also useful for detecting myocardial viability of dyssinergic segments, if an improvement of wall thickening is observed during the infusion of low-dose dobutamine (5 or 10 μg/kg/min) (4,5).

The echocardiographic markers of myocardial ischaemia and viability are mostly rather subtle and often difficult to detect unless 1) an optimal echo quality, and 2) an easiness of comparison between resting and stress imaging.

How can computer technology be useful for an easier and more efficient implementation of stress echocardiography?

Computer technology has played a crucial role in nearly all methods of cardiac imaging, including radionuclide imaging, X-ray computed tomography, magnetic resonance imaging and echocardiography (6-8).

The impact of computers has been on several aspects of cardiac imaging, like acquisition, formation, management, display, enhancement and analysis of the images.

The term digital stress echocardiography is a term indicating a combination of ultrasound and digital technology for a better acquisition, display, analysis, storage and retrieval of the echocardiographic results.

Videotape has become the medium which is universally used for recording two-dimensional echocardiograms. However, and in

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* Fioretti PM, Borden vd B, Arnese M, Vletter W, Linker DT.In:Computerized Echocardiography.Domenicucci S, Roelandt J, Pezzano A. (eds). Publisher: Centro Scientifico Editore,Torino, 1993; Pages:57-67.

particular in the setting of stress echocardiography, this has some disadvantages, compared to digital recordings (table 1).

Table 1

Digital cine-loop vs videotape recording in stress echocardiography

	Digital cine-loop	Videotape
Image quality	+++	++
Editing	+++	–
Interpretation	+++	+
Respiratory artefacts	–	++
Quantitative analysis	+++	++
Reporting	+++	+
Communication	+++	–
Diagnosis	++(+)	++
Echo monitoring	–	+++
Costs	+++	++

As also underscored by Feigenbaum (8), trying to analyze serial studies recorded on videotape is very cumbersome and time consuming. Salustri et al, from our group (9), has demostrated that the interpretation of dobutamine stress echo from videotapes and cine-loops provide a similar information in patients with normal or near normal wall motion at rest. However, the interpretation from cine-loops was quicker and easier. It is also expected that the interpretation from videotapes is even more cumbersome in patients with severe left ventricular dysfuncion and multiple dyssinergic regions, where too many wall motion abnormalities have to be memorized and compared.

By a proper selection of the best cardiac cycle, the generation of a continuous cine-loop of a single high quality cardiac cycle is also very helpful for the elimination of respiratory artifacts, which represents a major drawback in exercise echocardiography.

Also, the continuous cine-loop display will allow an unlimited time for review and facilitate a frame by frame analysis. This may improve the ability to detedt subtle wall motion abnormalities.

Another advantage of digital stress echocardiography is the possibility of a side by side display (Fig. 1) of different conditions (base vs peak stress, or at different stages of stress, especially during pharmacological stress), that may further refine the diagnosis on the presence and the timing of occurrence of wall motion abnormalities.

A continuous cine-loop recording is obtained by the use of a digital frame grabbing instrument. The sequence is initiated at the peak of the R wave of the electrocardiogram and subsequent frames are digitized at pre-set time intervals to allow the acquisition of the the

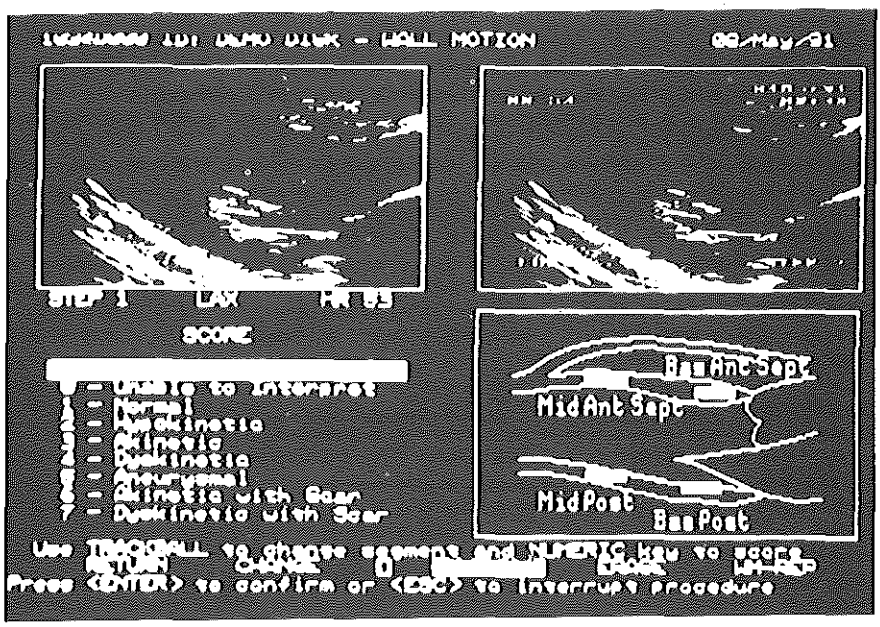


Figure 1 - Example of a side by side display of 2 cine-loops and scoring system for visual analysis.

whole systole and eventually some systems allow the display of the whole cardiac cycle.

There are different methods for the ECG triggering. The use of an external ECG signal has the greatest success rate and is the most reliable. In alternative, the use of the ECG signal on the video tape is a more difficult and less reliable method for triggering.

Time Compensation

If we compare two or more cine-loops side-by-side, the rate of contraction and time of end-systole are not synchronous, even though the start of systole has been synchronized using the ECG. If we collect the same number of images during the resting study and at peak exercise, we must lose part of systole during the rest study, or include part of diastole in the stress study (Fig. 2). This is due to the shortening of the cardiac cycle with stress. Full coordination of the loops we wish to compare should make it easier to detect abnormalities, although this has not been proven.

Technically, there are two ways which have been used to address this problem. The first is to adjust the rate of acquisition of frames based on the heart rate. At higher heart rates, the rate of frame acquisition would also be higher. During playback, the frame rates would be the same (Fig. 3). This gives a partial compensation for the changes in systolic duration, but it is not necessarily accurate, since

we know that diastole shortens more than systole at higher heart rates. This means that there will still be a residual asynchrony. The major advantage is that the compensation is completely automatic.

The second method is to acquire the images at a fixed rate, but to adjust the rate of playback so that the systolic period at rest and maximum stress are the same (Fig. 4). This cannot be completely automated, but has the advantage that it correctly adjusts both systole and diastole.

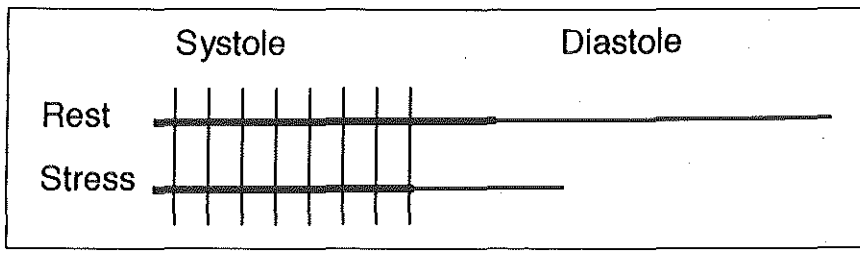


Figure 2

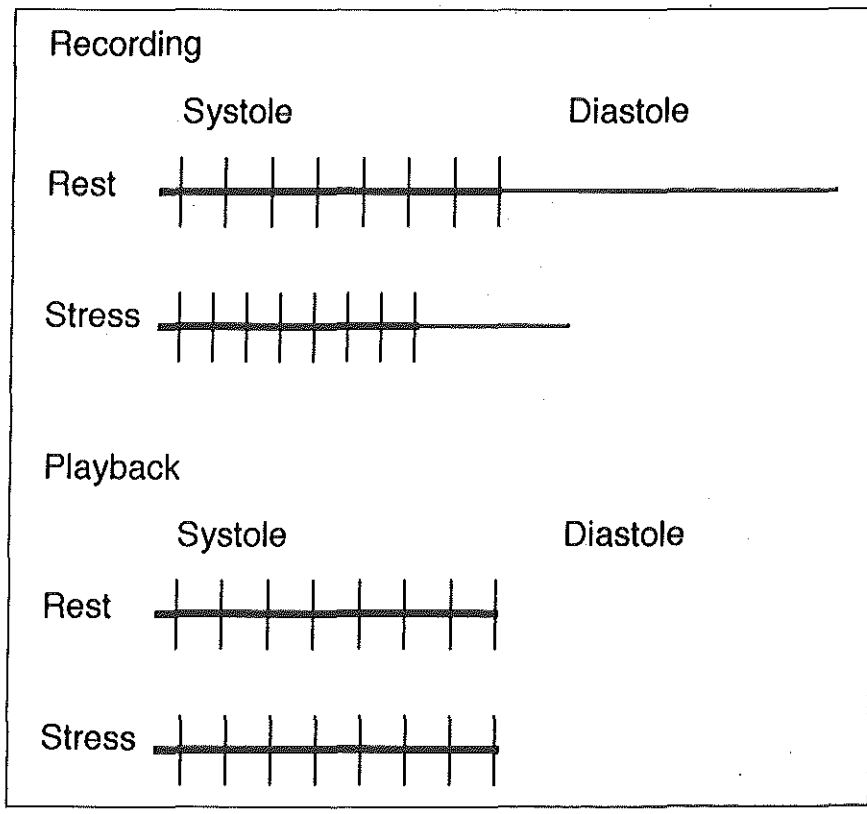
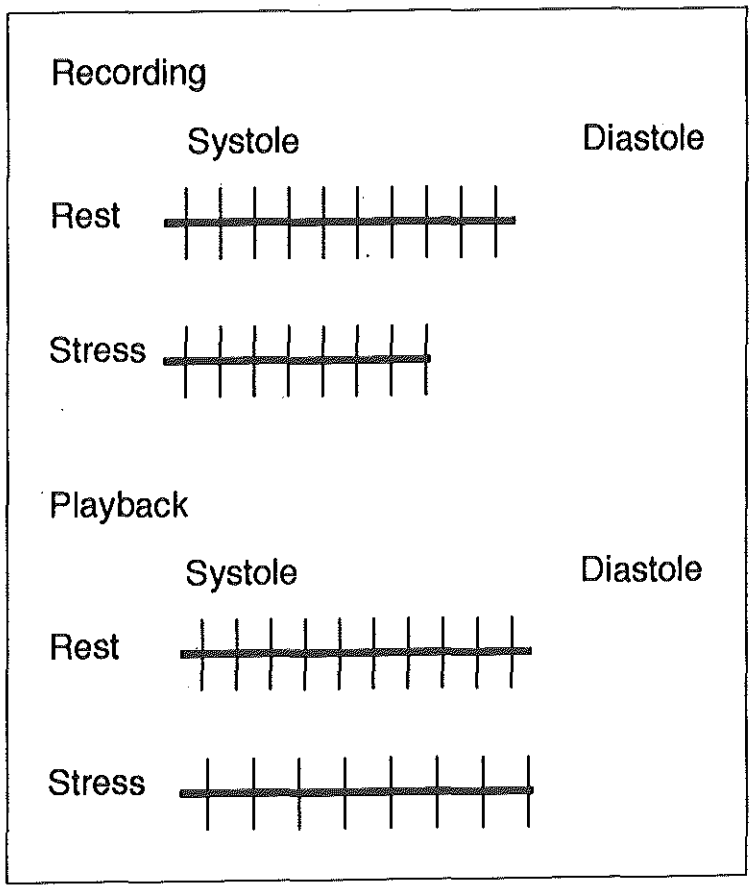


Figure 3



Figures 2 to 4 - Different solutions for time compensation in rest and stress images. For details see text.

Data acquisition

There are three different ways of collecting the echocardiographic data in digital form for analysis. Each has advantages and disadvantages. The simplest, conceptually, is to capture video directly from the ultrasound machine, using a second cable for the ECG triggering (Fig. 5). Second in complexity is using the ecg signal on the video itself for triggering (Fig. 6). This frees us from the constraint of only doing real-time acquisition. We can just as easily use images which have been recorded on video tape. The problem is that using the image for ECG triggering is more machine dependent, due to differences in ECG display on various machines, and therefore less reliable.

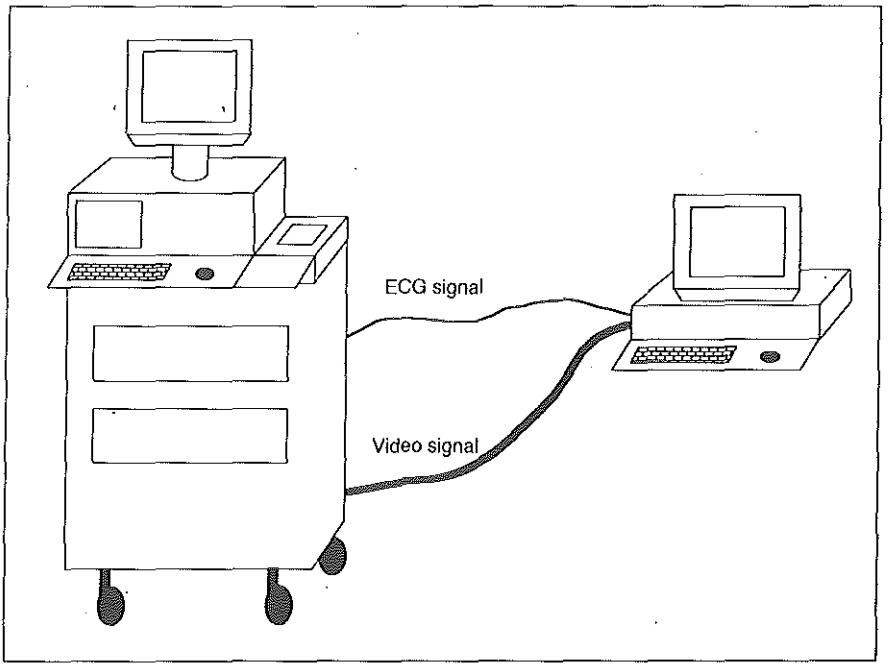


Figure 5

The last method avoids video altogether, by using a direct, digital data link to the electronics of the ultrasound machine itself (Fig. 7). This allows very high quality data to be captured, even at frame rates higher than video rates. The disadvantage is that it is only possible to capture data in real time, and the interface can only work with a specific ultrasound machine, due to internal differences.

There are some features of digital stress echocardiography in which the technology is not necessary, but helpful. Among them the possibility of scoring the regional wall motion while reviewing the cine-loops allows an automatic generation of a report and storage of the data (Fig. 1).

Further, it is also easier and faster to apply a quantitative analysis of regional wall motion on the cineloop systems. A quantitative assessment of regional wall motion has not become a part of the routine clinical practice. In view of the recent availability of softwares for the automated edge detection, it might happen that quantitative methods will be more widely used for the analysis of stress echocardiography.

The design of a digital stress echo system can be different: one possibility is its integration in the ultrasound instrument (in this case

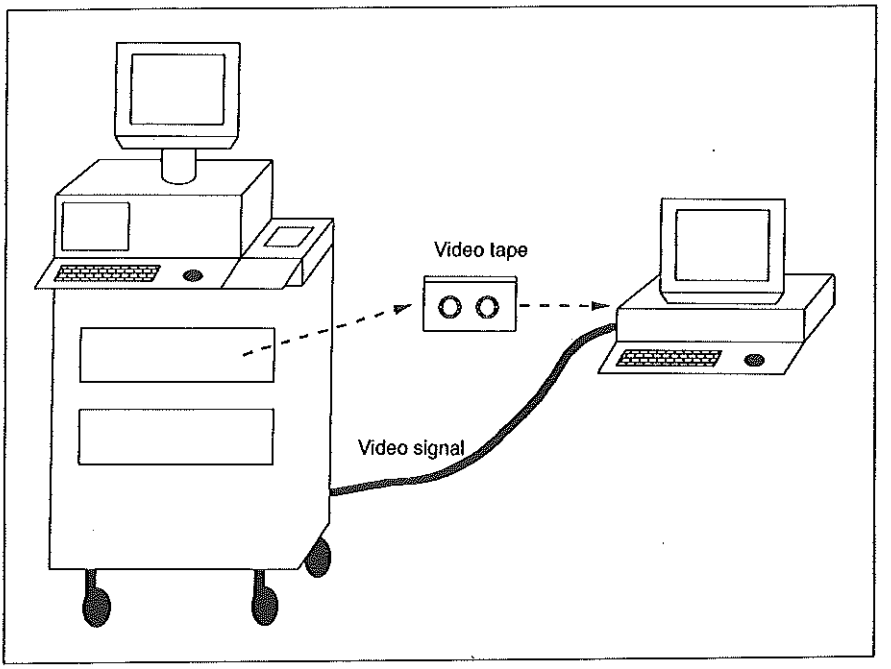
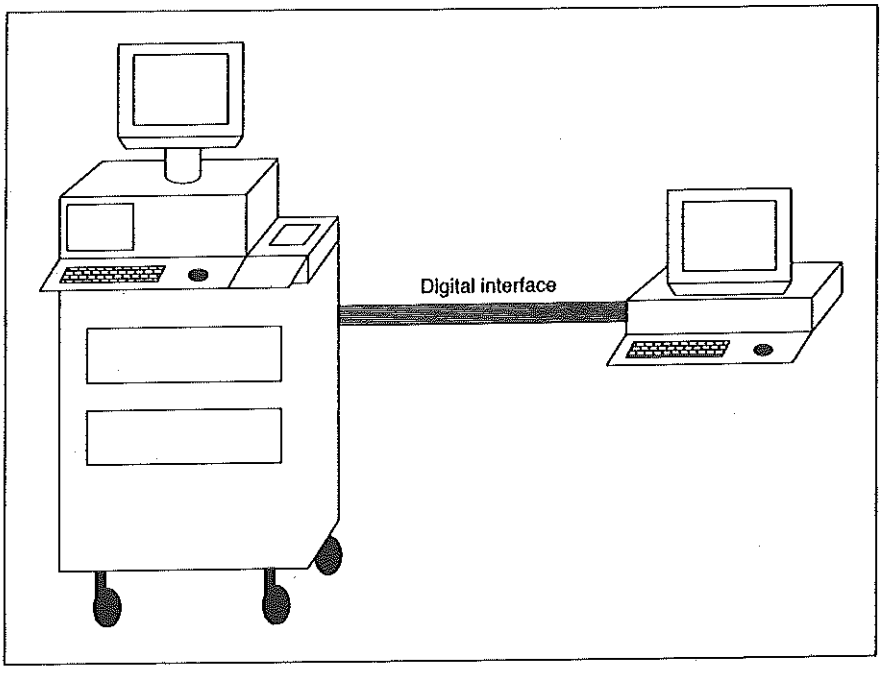


Figure 6



Figures 5 to 7 – Different solutions for data acquisition. For details, see text.

the acquisition will be optimized to the specific ultrasound instrument). The other possibility is to have a stand alone system.

A stand alone system can be dedicated to a specific ultrasound machine (useful if different echo machines of the same manufacturer) or universal (using a video signal).

The advantage of having a universal stand alone system is that of having the possibility of attaching this unit to any echo machine. Also, such a system allows to see the echo images being acquired with no interruption of the echo monitoring.

The integrated digital stress echo system can be also differentiated in two types, the first having a single monitor, for echo acquisition plus digital acquisition, and the second having 2 separate monitors, one for echo monitoring and the other for the digital acquisition and display.

Digital stress echocardiography also has major advantages compared to videotapes, for the greater efficiency in storage and retrieval of serial studies.

The review of serial studies from video tapes is extremely time consuming and tedious. This is a lesson that we have already learned from other imaging modalities, like nuclear cardiology: since the newest storage media like the optical disks are used, the retrieval and comparison of "old" studies for serial studies have become easier and frequently done. A similar trend is expected for stress echocardiography.

The relative merits of the individual storage media are summarized in table 2; the decision over the convenience of selecting one or the other should be based on the individual requirements and resources.

Another important issue is the usefulness of having a separate work station, to complement a digital stress echo machine. Hopefully, in the next future we will be able to use workstations for the storage and retriaeval not only of stress echo but of a complete clinical status. This will be incorporated in a comprehensive network (Fig. 8) including a variety of clinical information and images, like coronary angiography, nuclear studies and echocardiographic images.

In the future the costs, the format compatibility and a strict selection of the relevant clinical information will be crucial for the feasibility of the implementation of these new communication techniques (11).

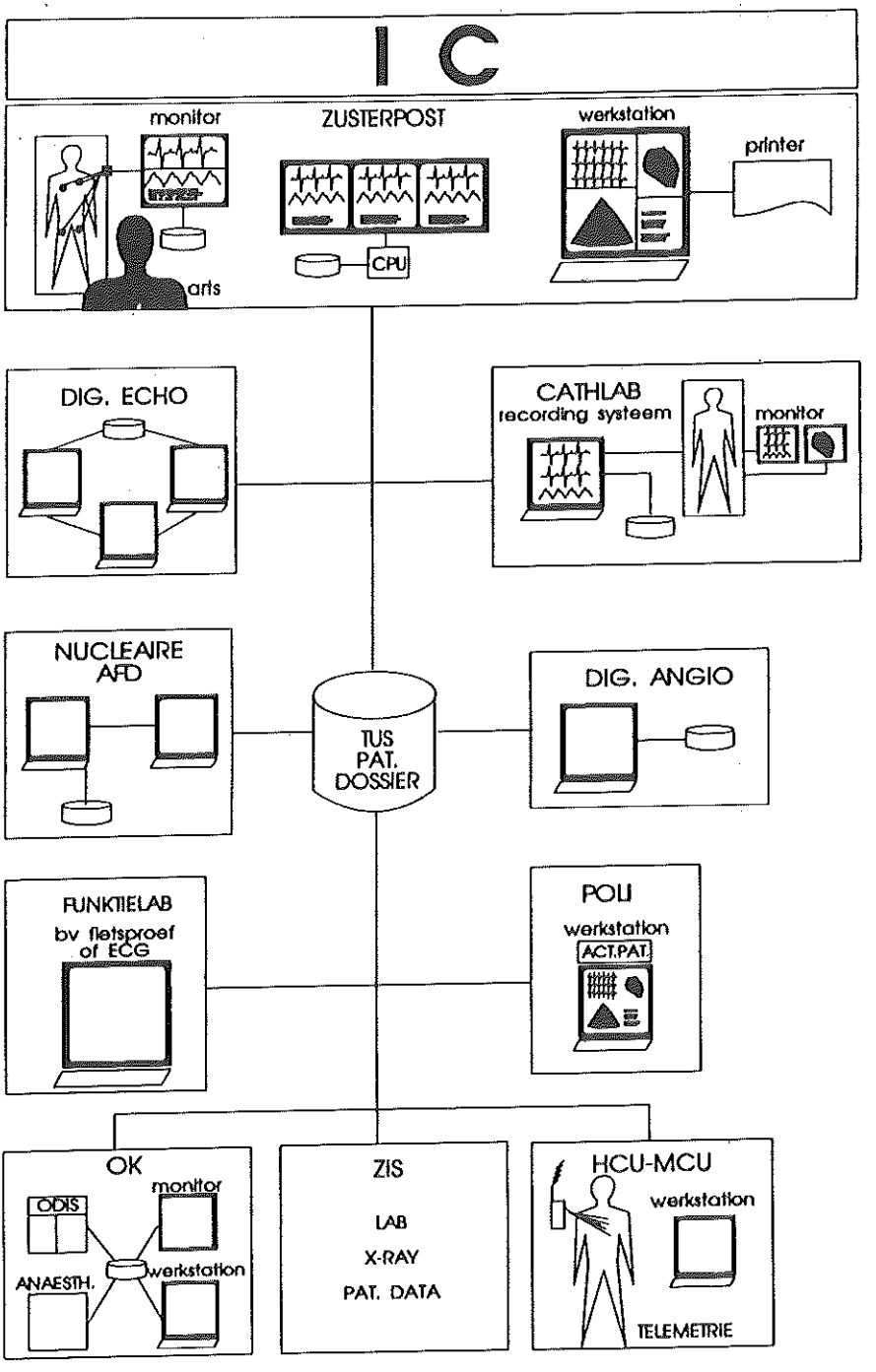


Figure 8 - Schematic representation of the electronic communication network planned at the Thoraxcentre.

Table 2

Digital stress echocardiography, storage and retrieve media

	Storage capacity	Retrieval speed	Price
Floppy disk	+	+	+
Hard disk	++	+++	++
Optical disk	+++	++	+++

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CHAPTER II

SAFETY OF DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED OR PROVEN CORONARY ARTERY DISEASE*

Summary

The purpose of this study was to establish the safety of high-dose dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. Six hundred fifty consecutive examinations were completed. Mean age of patients was 61 years; 300 had a previous myocardial infarction. Heart rate increased from 73 to 129 beats/min during stress testing, blood pressure did not change significantly (from 140/81 to 150/80 mm Hg. Atropine was added to dobutamine in 239 patients when no ischemia was induced with dobutamine alone and the peak heart rate was <85% of the theoretical maximal heart rate. Atropine was more frequently administered to patients taking β-blockers (77 vs 27 %, $p< 0.001$). New wall motion abnormalities developed in 243 patients (37%). Significant or symptomatic cardiac tachyarrhythmias, or both, developed during 24 examinations: 1 patient developed ventricular fibrillation, 3 patients developed sustained ventricular tachycardia (< 10 beats) and 8 patients had paroxysmal atrial fibrillation. Cardiac arrhythmias were more frequent in patients with a history of ventricular arrhythmias (ventricular tachycardia and fibrillation) (odds ratio 9.9, 2.0 to 45) or left ventricular dysfunction at rest (wall motion score $\geq$ 1.12) (odds ratio 2.9, 1.1-7.6), but not associated with atropine addition. No death or myocardial infarction occurred. The full dose was not given to 13 patients despite absence of signs or markers of ischemia for limiting side effect, yielding an overall feasibility of the stress test of 98%. Thus, dobutamine-atropine stress echocardiography is relatively safe and highly feasible test with few adverse effects; its highest risk of significant arrhythmias occurs in patients with a history of ventricular arrhythmias or left ventricular dysfunction, or both.

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* Poldermans D, Fioretti PM, Boersma E, Forster T, Van Urk H, Cornel JH, Arnese M, Roelandt JRTC. Am J Cardiol 1994;73:456-459.

Introduction

Dobutamine-atropine stress combined with echocardiography was recently proposed for the diagnosis of coronary artery disease (1). The test provides diagnostic information (2-4). High-dose dobutamine is potentially arrhythmogenic: hypotension has been report to occur, and the safety of adding atropine to potentiate the test has not been extensively reported. So far only the study of Mertes et at (5) has described the results of a large series of patients on the safety and hemodynamic effect of the test. The aim of the present study is to describe the safety, feasibility and adverse effects of dobutamine stress echocardiography, particularly when atropine is used for the potentiation of the dobutamine stress test (1-3,6).

Methods

Patients characteristics: Six hundred fifty-two examinations were attempted in 626 consecutive patients (494 men, mean age 61 years, range 22 to 90) with known or suspected coronary artery disease. A previous myocardial infarction was present in 300 patients. Angina pectoris was present in 281 patients. Antianginal medication was non discontinued before the study, including b blocker medication in 268 cases. Indication for examinations were chest pain evaluation (n=440) and preoperative cardiac risk stratification before non-cardiac surgery (n=212).

Dobutamine stress echocardiography: The dobutamine stress echocardiography protocol was approved by the hospital ethics committee and was performed as described previously (1). Briefly, after giving verbal informed consent, patients underwent a resting 2-dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape and a 12-lead electrocardiogram was recorded. Dobutamine was then administered intravenously by infusion pump, starting at 10 µg/kg/min for 3 minutes, increasing by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age-predicted maximal heart rate (in men [220-age] x 85%, in women [200-age] x 85%) who had no symptoms or signs of ischemia, atropine (beginning with 0.25 mg and increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine infusion was continued. Throughout dobutamine infusion the electrocardiogram was continuously monitored, the 12-lead electrocardiogram was recorded each minute and blood pressure was measured by sphygmomanoemtry every 3 minutes. The 2

dimensional echocardiogram was continuously monitored and recorded on video tape during the final minute of each stage. Quad screen display for side-by-side examination of rest and stress images have become routine during the last 200 studies. Metroprolol was available and used (1 to 5 mg intravenously) to reverse the effects of dobutamine or dobutamine-atropine combination if these did not revert spontaneously and quickly. Atropine was also used as an antidote if bradycardia occurred after dobutamine. Off-line assessment of echocardiographic images was performed by 2 experienced investigators without knowledge of the patients' clinical data but with knowledge of the doses of dobutamine and atropine used. For this semiquantitative assessment the left ventricular wall was divided into 14 segments (7) and each was scored using a 4-point scale: 1= normal, 2= hypokinetic, 3= akinetic, 4= dyskinetic. Wall motion score index at rest (total score divided by the number of assessable segments) was calculated for each patient. An increase in score between rest and stress in 1 or more segments, which is a new or worsened wall motion abnormality, constituted a positive test.

Interruption criteria for the test were a horizontal or downsloping ST depression > 2 mm at 80 ms after the J point, ST elevation, significant chest pain, reduction in systolic blood pressure > 40 mmHg from that at rest or systolic blood pressure <100 mm Hg, significant cardiac arrhythmias, or any side effect regarded as being due to dobutamine. A new wall motion abnormality was considered as an interruption criteria in absence of adverse effects or other markers of ischemia only if it was severe or extensive.

Statistical analysis: Univariate analysis for categorical variables was performed using chi-square test with Yates'correction or Fisher's exact test. Continuos variables were analyzed using Student's *t* test. The difference in risk was expressed as the odds ratio (OR) with the corresponding 95% confidence intervals (CI).Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. To compare and visualize the predictive value for cardiac arrhythmias of wall motion score index at rest, we used receiver-operator characteristics curves.

Results

The dobutamine-atropine stress test was attempted 652 times. In 13 cases the test was nondiagnostic because it was prematurely stopped despite absence of signs or markers of ischemia for limiting side effects (chills [n=6], hypotension [n=2], hypertension [n=1], cardiac arrhythmias [n=2] and poor echo images [n=2], yielding an overall

feasibility of the test of 98%. There were no deaths or myocardial infarctions.

In 587 tests (90%) the target heart rate (85% of theoretic maximal heart rate) was reached. During 63 examinations, the following symptoms caused the test to be stopped: (1) severe chest pain in 30 patients (4.6%); (2) electrocardiographic changes in 9 patients (1.4%); (3) new wall motion abnormalities in 1 study (0.2%); (4) hypertension (systolic blood pressure => 220 mm Hg) in one patient (0.2 %); (5) hypotension (systolic blood pressure decrease > 40 mm Hg compared with baseline) in 4 patients (0.6%); and (6) cardiac arrhythmias (ventricular fibrillation in 1, sustained ventricular tachycardia in 3, and paroxysmal atrial fibrillation in 8) in 12 patients (1.9%) and chills in 6 (0.9%).

Patients were divided into 2 groups: the first group (n=411) received dobutamine alone and the second (n=239) received dobutamine plus atropine. A comparison of clinical characteristics, adverse effects and reasons for stopping the test in the 2 groups are presented in Table I and II. Atropine was administered more often in patients taking β-blocker medication (OR 5.4, 95% CI 3.8 to 7.9).

TABLE I Clinical Characteristics in Patients With and Without Atropine

Clinical Data	Group I (n = 411)	Group II (n = 239)	
Age (years) ± SD	63 ± 12	58 ± 12	
	p = 0.0001		OR, 95% CI
β blockers (%)	110 (27)	158 (66)	5.4, 3.8–7.9
History of angina (%)	165 (40)	116 (48)	1.3, 0.9–1.8
History of infarction (%)	184 (45)	116 (48)	1.1, 0.6–1.7
Diabetes mellitus (%)	33 (8)	19 (8)	1.0, 0.5–1.9
Male sex (%)	308 (75)	186 (78)	0.9, 0.6–1.3

CI = confidence interval; Group I = stress test with dobutamine alone; Group II = dobutamine stress test with addition of atropine; OR = odds ratio.

One or more markers of ischemia were detected during the test in a substantial proportion of patients: as ischemic ST depression (≥1 mm) was documented in 151 patients (24%) and ST elevation in 57 patients (9%). Chest pain was seen in 145 patients (22%) and new or worsening wall motion abnormalities in 243 patients (37%).

Hemodynamic changes during dobutamine-atropine stress test: Heart rate and blood pressure values during stress test are listed in Table III. There was no significant change in blood pressure during peak stress.

TABLE II Comparison of Adverse Effects and Reasons for Stopping Stress Test in Patients With and Without Atropine

	Group I (n = 411)	Group II (n = 239)	OR, 95% CI
Adverse Effects			
Arrhythmias (%)	15 (3.6)	9 (3.7)	1.1, 0.4–2.8
Chills (%)	7 (1.7)	5 (2)	1.1, 0.3–2.7
Hypotension			
20–40 mm Hg (%)	23 (5.6)	7 (2.9)	0.8, 0.4–1.5
>40 mm Hg (%)	2 (0.5)	2 (0.8)	1.4, 0.5–3.7
Hypertension	1 (0.2)	0	
Interruption Criteria			
Target heart rate (%)	379 (92)	214 (90)	1.2, 0.7–2.3
Hypotension >40 mm Hg (%)	2 (0.5)	2 (0.8)	1.8, 0.2–12.3
Arrhythmias (%)	6 (1.4)	6 (2.5)	1.7, 0.5–5.4
Angina pectoris (%)	19 (4.6)	11 (4.6)	1.2, 0.8–1.7
ECG changes (%)	3 (0.7)	6 (2.5)	1.1, 0.8–1.5
NWMA (%)	1 (0.2)	0	
Hypertension (%)	1 (0.2)	0	

Arrhythmias = ventricular fibrillation, sustained ventricular tachycardia (>10 beats), nonsustained ventricular tachycardia (<10 beats) and paroxysmal atrial fibrillation; ECG = electrocardiographic; Hypotension = decrease in systolic blood pressure compared with baseline; NWMA = new wall motion abnormalities; other abbreviations and explanations as in Table I.

Side effects: Hypotension and cardiac arrhythmias were the 2 most observed side effects of the stress test.

Hypotension, when defined as a decrease in systolic blood pressure of > 20 mm Hg compared with baseline, occurred during 34 (5.2%) examinations. Although most patients were able to continue the test without discomfort, 4 discontinued the test because of severe hypotension (decrease in systolic blood pressure > 40 mmHg). There was no correlation between hypotension and clinical data or stress results, but patients with concurrent b-blocker medication had significantly less hypotension (OR 4.1, 95% CI 2.1 to 8.7). Hypotension was not related to the dose of dobutamine (OR 0.8, 95% CI 0.4 to 1.7), nor was it alleviated by the addition of atropine (OR 1.2, 95% CI 0.7 to 2.1). In 7 patients with a systolic blood pressure decrease of 20 mm Hg during large-doses of dobutamine, atropine was added without inducing more adverse effects compared with a similar group of 23 patients without atropine (OR 1.2, 95% CI 0.3 to 5.0).

Significant or symptomatic cardiac tachyarrhythmias, or both, occurred in 24 examinations: Besides arrhythmias leading to

TABLE III Hemodynamic Effects of Dobutamine-Atropine Stress Test

	Group I (n = 411)	Group II (n = 239)
Heart rate (beats/min)		
Rest	75 ± 14	66 ± 12*
Dobutamine	129 ± 19	95 ± 22*
Dobutamine + atropine	—	129 ± 18†
Systolic BP (mm Hg)		
Rest	142 ± 25	135 ± 22*
Dobutamine	153 ± 32	146 ± 25*
Dobutamine + atropine	—	149 ± 27†
Diastolic BP (mm Hg)		
Rest	82 ± 13	79 ± 12‡
Dobutamine	79 ± 17	72 ± 21*
Dobutamine + atropine	—	78 ± 13†

*p value < 0.001 between groups II and I at the same stage.
†No significant difference between peak dobutamine (group I)/dobutamine + atropine (group II).
‡p value = 0.02 between groups II and I at the same stage.
Data are expressed as mean ± SD.
BP = blood pressure; other explanations as in Table I.

interruption of the test, 12 patients experienced nonsustained ventricular tachycardia. Ventricular premature complexes occurred in 64 examinations and was not considered as a serious side effect. The patient with ventricular fibrillation had previous symptomatic ventricular arrhythmias and myocardial infarction. Wall motion score index at rest was 1.56. During dobutamine infusion (40 μg/kg/min), this patient developed new wall motion abnormalities, rapidly followed by ventricular fibrillation, and was successfully resuscitated (1 single countershock) without evidence of a new cardiac infarction. Sustained ventricular tachycardia occurred in 12 patients at a heart rate of 160 to 180 beats/min, lasting no > 2 minutes, and abated by metoprolol instantly in 2. There was no occurrence in the hours after the test.

The incidence of dobutamine-induced cardiac arrhythmias was increased in patients with a history of previous ventricular arrhythmias (ventricular tachycardia or fibrillation) (OR 9.9, 95% CI 2.0 to 45) at rest wall motion abnormalities, defined as resting with wall motion score index $\geq$ 1.12 (OR 2.9, 95% CI 1.1 to 7.6). Other stress test results, including the ischemic signs or markers were no predictive of arrhythmias. There was no correlation between atropine addition and arrhythmias (OR 1.2, 95% CI 0.4 to 3.3). Bradycardia accompanied by hypotension occurred in 2 patients, both with stress-induced inferior wall ischemia. Both patients were given atropine (0.25 mg intravenously) and recovered without complications.

Discussion

Dobutamine-atropine stress is a new and promising test for the detection of coronary artery disease. During 652 examinations the test was not completed in 16 patients despite absence of signs or markers of ischemia for limiting adverse effects, yielding an overall feasibility of 98%. These results are comparable with dipyridamole echocardiography (8), which showed a feasibility of 99%.

Target heart rate as test end point was reached in 90% of the examinations. This is higher than studies, such as that of Mertes et al (5) in which target heart rate was achieved in 52% and that of Mazeika et al (9) in which it was reached 18%. This can be partly explained by a different stress protocol because there was no interruption for (1) "moderate" hypotension (decrease in systolic blood pressure $\geq$20 mmHg to < 40 mm Hg compared with baseline); and (2) new wall motion abnormalities unless severe and extensive or accompanied by other markers of ischemia, and atropine was always given to patients who were unable to reach test end point (target heart rate or any sign or marker of ischemia). Despite this more "aggressive" approach there were no fatal complications or myocardial infarctions.

Adverse effects consisted mostly of hypotension and cardiac arrhythmias. Hypotension, if defined as a decrease in systolic blood pressure of > 20 mm Hg, is the most frequent adverse effect (34 examinations), leading to a premature end of the test in only 4 instances in which systolic blood pressure decrease > 40 mm Hg compared with baseline value. We do not consider a systolic blood pressure decrease of $\geq$20 to <40 mm Hg during the test has a serious side effect, in contrast to other investigators (9,10). In our experience there were no complications as long as the patient is monitored closely and can be given atropine safely if the target heart rate is not reached with dobutamine alone.

Possible mechanisms of dobutamine-atropine-induced hypotension are (1) poor left ventricular function during stress because of extensive wall motion abnormalities, (2) vasodilator effect of dobutamine, (3) development of subaortic stenosis, (4) atropine administration, and (5) vasodepressor reflex induced by vigorous contractions as suggested by Mazeika et al (11). Our findings support options 2 and 5. Similar to others (12, 13), we observed that hypotension occurred less frequently in patients taking β-blockers.

Cardiac arrhythmias are the second most noted adverse affects. Our study shows an incidence of significant arrhythmias (ventricular fibrillation, sustained/nonsustained ventricular tachycardia, atrial fibrillation/atrial flutter) in 24 patients (3.6%), similar to the study of Mertes et al (5), who found an incidence of 48 of 1,118 (4,3%). There

was a strong relation between a history of previous ventricular arrhythmias (ventricular tachycardia or fibrillation) or diffuse wall motion abnormalities at rest (both indicating a poor left ventricular function) and cardiac arrhythmias during the test. There was no correlation with signs or markers of ischemia during the test or with the addition of atropine.

In conclusion, dobutamine-atropine stress echocardiography is a safe and feasible test. Some caution should be used in patients with a history of ventricular arrhythmias or poor left ventricular function at rest, in whom the test may induce serious arrhythmias. In these patients comparative studies with other stress modalities like dipyridamole are required.

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CHAPTER III

ANALYSIS OF INTERINSTITUTIONAL OBSERVER AGREEMENT IN THE INTERPRETATION OF DOBUTAMINE STRESS ECHOCARDIOGRAMS*

Abstract

Objectives: The degree of interinstitutional agreement in the interpretation of dobutamine stress echocardiograms was to be determine .

Background: Dobutamine stress echocardiography involves subjective interpretation. Consistent methods for acquisition and interpretation are critically important for obtaining high interobserver agreement and for facilitating communication regarding the results of a test.

Methods: Five experienced centers were asked to each submit 30 dobutamine stress echocardiograms (dobutamine up to 40 µg/kg/min and atropine up to 1 mg) performed on patients undergoing coronary angiography. Thus, a total of 150 dobutamine stress echocardiograms were interpreted by each center unaware of any other patient data. Left ventricular wall motion was assessed using a 16 - segment model but was otherwise not standardized. No patients were excluded due to low image quality or inadequate stress level. Echo image quality was assessed on a five point scale.

Results: Angiographically significant coronary artery disease (>50% diameter stenosis) was present in 95 patients (63%): based on a majority decision (3 or more centers), the sensitivity, specificity and accuracy of dobutamine echocardiography were respectively 76%, 87% and 80%. Abnormal or normal results of stress echocardiography were agreed upon 4 or 5 of the five centers in 73% of patients (mean kappa = 0.37). Agreement on the LAD territory (78%) was similar compared with the combined RCA/LCX territory (74%) and for specific segments the agreement ranged from 84% to 97%, being highest for the basal anteriorl segment and lowest for the basal inferior

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segment. Agreement was higher in patients with no coronary artery disease (82%) and in patients with 3 vessel disease (100%), and lower in patients with 1 and 2 vessel disease (61 and 68%, respectively). For those patients with highest image quality agreement on positively or negativity of a stress test was 100% while it was only 43% for those with the lowest image quality ($p = 0.003$).

Conclusions: The current heterogeneity in data acquisition and reading criteria between different centers results in a rather low interinstitutional agreement in interpretation of stress echocardiograms. Agreement is higher in patients either without or with advanced coronary artery disease and substantially lower in patients with limited echo image quality. To increase interinstituional agreement, a better standardization in image acquisition and reading criteria of stress echocardiography is recommended.

Introduction

Dobutamine stress echocardiography is an accurate non - invasive technique for the diagnosis of coronary artery disease (1,2). As the assessment of improvment or deterioration of regional wall motion during the test is subjective, not only the accuracy but also the agreement between interpreters are important considerations in the expansion of the test to the clinical arena. This is because inter-observer agreement influences the ability of physicians to communicate with each other regarding the test results and their therapeutic implications.

Most diagnostic methods have been examined for observer variability of assessment including clinical examination (3, 4), ECG (5, 6), exercise ECG (7), perfusion scintigraphy (8) and coronary angiography (9,10). Wall motion analysis by means of echocardiography is an example of the difficulty with interobserver agreement because interpretation of test results is inherently subjective. The interobserver variability of stress echocardiography has already been examined in a small patient groups (11) but this study was confined to readers from the same institution and the results may have been influenced by local standards and conventions not explicitly stated, which may influence diagnostic decisions expecially in border line situations. To circumvent these considerations we designed a multicenter study to assess the interobserver agreement of experienced readers from diffrent institutions in interpreting dobutamine stress echo images without any additional clinical data. This report presents the analysis of agreement within a panel of five readers who independently read 150 dobutamine stress echo studies submitted in equal shares by all five institutions.

Methods

Patients. At each of the five institutions thirty consecutive patients scheduled for angiography due to suspected coronary artery lesions underwent dobutamine stress echocardiography.

The results of strress echocardiography did not influence the decision to perform angiography. No patients were excluded of basis of poor echocardiographic image quality. Patients with prior Q-wave myocardial infarction were not included in the study, as well those with congestive heart failure, severe congenital or acquired valvular heart disease, or documented cardiomyopathy. A total of 146 patients were investigated, 4 patients underwent a second examination after interventional therapy had been performed. There were 116 men and 30 women with a mean age of 46±12 years. Previous myocardial revascularization had been performed in 26 patients (20 with coronary angioplasty and 6 patients with coronary artery bypass grafting) and 14 patients had non-Q-wave infarction. One-hundred thirteen patients had angina at the time of examination. Antianginal therapy prior to the examination consisted of nitrates in 78 patients, calzium channel antagonists in 48 patients and beta-receptor blockers in 45 patients. In 39 patients antianginal medication was stopped prior to stress echocardiography.

Dobutamine stress protocol. Dobutamine was infused intravenously, starting at a dose of 5 µg/kg/min for 3 minutes, increasing the dosage every 3 minutes to 10, 20, 30 and 40 µg/kg/min.

In case 85% of age predicted maximal heart rate was not reached, additional atropine was given intravenously in 0.25 mg steps every minute, up to a maximal dosage of 1.0 mg. The infusion was stopped before reaching maximal pharmacological stress for any of the following reasons: the development of new wall motion abnormalities, progressive and severe angina, more than 0.3 mV of downsloping ST-segment depression, the development of symptomatic hypotension (decrease in systolic blood pressure $\geq$ 20 mm Hg), significant hypertension (systolic blood pressure > 240 mmHg), dyspnoe or severe ventricular arrhythmias.

Monitoring. Blood pressure and 12-lead ECG recordings were performed at baseline and at the end of each dobutamine stage or before the premature cessation of the test. The presence of horizontal or downsloping ST-segment depression of a least 0.2 mV, 0.08 sec after the J-point compared with baseline was considered diagnostic for myocardial ischemia. The double product was calculated by multiplying systolic blood pressure and heart rate.

Image acquisition. Image acquisition was performed with the patient in the left lateral decubitus position before, during and after dobutamine infusion. No patient was excluded because of low image quality. In each patient, imaging was attempted in the parasternal long-axis and short-axis as well as the apical four-chamber and two-chamber views: in 32 patients, one or more views were not recorded because of insufficient acoustic windows. All views obtained at baseline were re-acquired at the end of each dobutamine stress level and when new wall motion abnormalities or worsening of pre-existing wall motion abnormalities occurred; however, only the images at rest and peak stress conditions were selected and stored for exchange. Individual centers maintened their standard practice for image acquisition , so that in 82 patients (from 3 centers) images were recorded on video tape only, and in 68 patients (from 3 centers) images were digitized on-line into a quad-screen cine-loop format. In all cases, recorded images were transferred to SVHS-video tapes to have a uniformly readable media and distributed to all centers for interpretation

For those studies being primarily digitized and transfered onto video direct comparison of resting and stress images in the a quad-screen cine-loop format was still possible because long session of the digitized images were taped.

Stress echo interpretation To base interpretation exclusively on imaging data, each of the 5 centers evaluated all 150 dobutamine stress investigations using a standardized report form without knowledge of any patient data apart from the echo images. Thus, no information on maximal dobutamine/atropine dosage and reason for termination of the dobutamine stress test was given. Clinical or angiographic data of these patients were also not available.

For the analysis for wall motion the left ventricular walls were divided according to a 16-segment model (Figure 1). The two region distribution of coronary circulation was used for further analysis of segmental wall motion abnormalities related to coronary circulation with segments 3, 6, 7, 9, 10, 11, and 12 being part of the combined right coronary/left circunflex territory, opposed to the left anterior descending territory including the rest of the segments. Segmental wall motion was evaluated and scored according to the method of the American Society of Echocardiography as normal (score of 1), hypokinetic (score of 2), akinetic (score of 3), or dyskinetic (score of 4). The dobutamine stress echocardiogram was considered positive if the score increased by a least one level in at least one segment with stress. Resting wall motion abnormalities not deteriorating with stress were not considered as positive test results.Other interpretive criteria were not stipulated.

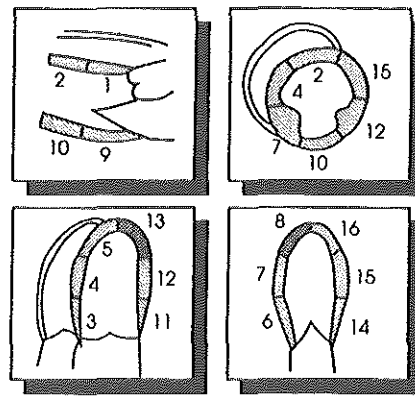


Figure 1 - Sixteen-segment scheme according to regional wall motion evalutation with a two-region distribution of coronary circulation. **Leftward hatching** = left anterior descending distribution; **rightward hatching** = right coronary/left circumflex distribution; **numbers** are segment numbers.

Echo image quality was assessed by the co-ordinating center for each stress test on a five point scale whereby an A quality showed complete endocardial definition and wall thickening with exactly similar images views at rest and during dobutamine, an B quality allowed visualization of all segments, however not completely fulfilling the before mentioned criteria, a C quality did not allow detection of one or two segments, but adjacend segments within the same territory could be visualized, a D quality did not allow interpretation of 3 or more segments, but adjacend segments of the same territory could be visualized, an E quality precluded interpretations of segments comprising one or more whole territories.

Coronary angiography and angiopraphic analyses. The coronary anatomy of all patients was evaluated by coronary angiography, with the degree of coronary artery stenoses being determined by caliper method in at least one projection. Significant coronary artery stenosis was considered present when $\geq$ 50% reduction of vessel diameter was observed in at least one major coronary artery.

Statistical analysis. Calculations of sensitivity, specificity and diagnostic accuracy of dobutamine stress echocardiography for the detection of significant coronary artery disease were performed on the basis of the majority opinion (three or more centers). In addiction calculation were also persormed with the criteria of a $\geq$ 70% luminal diameter narrowing.

Concordant interpretation was identify in the presence of identical readings in 4 or 5 of the five interpreting centers. In addition to

analyzing the overall agreement of dobutamine stress echocardiograpphic interpretation between all institution, the role of variation in acquisition and interpretation were investigated by focusing on echocardiograms submitted and interpreted at individual institution, respectively.

The influence of severity of coronary artery disease, echo image quality and the recording system on the reproducibility of data were similarly recorded.

The kappa test was used to test the hypothesis that agreement was greater than chance alone (12). Average coefficients of agreement (kappa) were computed for the five readers of the different institutions.

Results

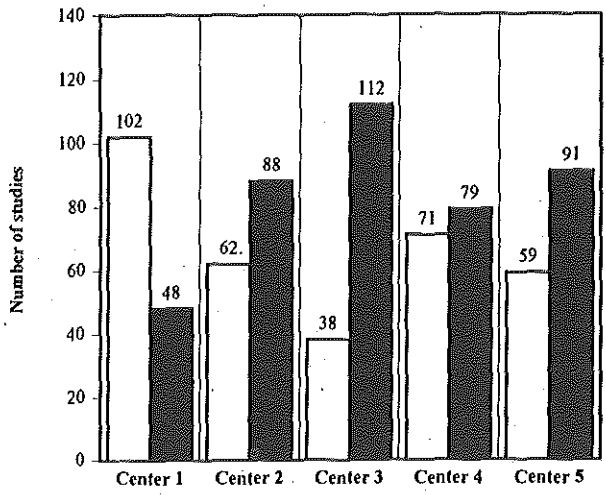
Coronary angiography. Coronary angiography identified significant coronary artery disease in 95 patients. One-vessel disease was seen in 59 patient (62% of those with significant coronary artery disease), two-vessel disease in 22 patients (23%) and three-vessel disease in 14 patients (15%). Distribution of affected vessels was: left anterior descending coronary artery in 62 (41%), circumflex artery in 33 (22%), and right coronary artery in 50 (33%) patients. Bypass graft stenosis was counted equivalent to stenosis of the grafted native vessel.

Dobutamine stress test. The average maximal dobutamine dosage was 35±8.3 μg/kg/min. In 53 patients additional atropine was given. This resulted in an increase of the heart rate from 67±12 (range 45-105) beats/min at baseline to 122±27 (range 40-210) beats/min at peak stress. Double product increased from 10964±2623 mmHg min^{-1} to 20136±5245 mmHg min^{-1} with maximal pharmacological stress.

Fifty-seven patients developed angina during the stress test. Dobutamine stress was stopped prematurely in 37 patients. Significant ECG-changes with maximal stress developed in 41 patients.

Echocardiography. There was a significant difference between the centers in identifying dobutamine stress tests as positive. On an average 67 stress tests were evaluated as being positive, but these results ranged from 38 to 102 between centers (figure 2).

Sensitivity, specificity and diagnostic accuracy. Using majority opinion (three or more) of the 5 centers to define the presence of positive or negative results in all 150 patients, dobutamine stress echocardiography had a sensitivity of 76% for the detection of significant coronary artery disease. When studies submitted by



Figre 2 - Evaluation of negativity **(solid bars** versus positivity **(open bars)** for the 150 dobutamine stress echocardiograms by institution. **Numbers above bars** = number of patients.

different Institutions were compared, the sensitivity ranged from 67% to 79% . The average specificity was 87% (range: 73-100%) and accuracy for detection of coronary artery disease was 80% (range 77% to 87%). Regarding those lesions having a $\geq$ 70% diameter stenosis, sensitivity, specificity and accuracy were: 83%, 83% and 83%, respectively.

Agreement between institutions. For or five of the five institutions agreed on dobutamine stress test abnormality or normality in 110 of the 150 studies (73%). The average coefficient of agreement among readers from different institutions for normality or abnormality of dobutamine echo stress test (kappa) was 0.37. For those 31 studies in whom the majority of the observer identified a baseline wall motion abnormality majority agreement was slightly smaller (71%) than for those 119 studies without baseline wall motion abnormality (74%).

Considering only those left ventricular segments supplied by the left anterior descending artery agreement concerning the presence or absence of new wall motion abnormalities was 78% (mean kappa = 0.37), similar to the combined RCA/LCX territory in whom a majority agreement of 74% (mean kappa=0.33) was reached. Agreement in specific segments ranged from 84% to 97%, being highest for anterior segment (segment 14 on the 16 segment model) and lowest for the basal inferior segment (segment 6 on the 16 segment model) (Figure 3).

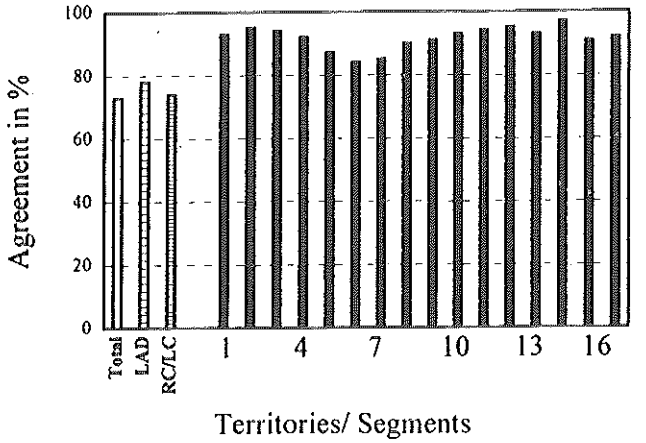


Figure 3 - Majority interinstitutional agreement on a four of five or five of five basis for positivity or negativity of dobutamine stress test results by specific coronary territory and for each of 16 ventricular segments. LAD = left anterior descending coronary artery; RC/LC = right and left circumflex coronary arteries.

Agreement corresponding to disease severity. For patients having no coronary artery disease (n= 55) majority agreement on the dobutamine stress echo result was 82% on a 4/5 or 5/5 basis. In those patients having a three-vessel disease (n=14) majority agreement was 100% exceeding the concordance of results in patients having only a one-vessel or two-vessel disease (Figure 4).

Agreement omitting one analysing institution. Due to the observation that the centers had different rates of positive stress echo evaluations the agreement on dobutamine stress echo positively or negativity was evaluated for the remaining four centers after omitting

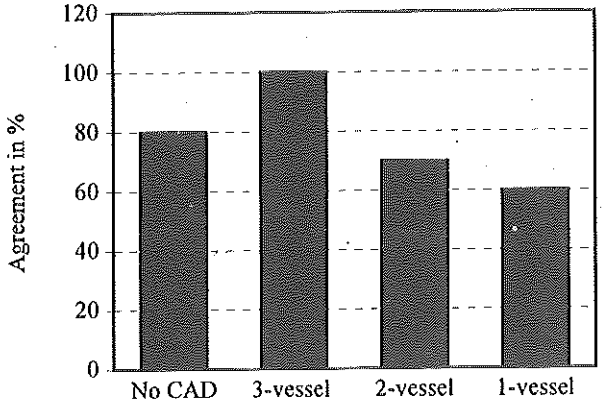


Figure 4 - Majority interinstitutional agreement on positivity or negativity of dobutamine stress echocardiographic results by severity of coronary artery disease (CAD)

the interpretations of one center. Majority agreement (3/4 or 4/4 centers) on overall positively or negativity increased for the remaining institutions each time one of the centers was omitted. However, there were quite different increases in agreement related to the agreement of all five center (73%). Agreement of 3/4 or 4/4 centers ranged between 77% and 87% depending on which of the five analysing centers was omitted (Figure 5).

Agreement on dobutamine stress tests submitted by single centers. In order to analyse whether dobutamine echo stress tests submitted by one institution were better interpretable and thus resulted in higher agreement than those of other institutions, the majority agreements for the 30 dobutamine echo tests submitted by each of the five institutions were analysed separately. Majority agreement on the 30 dobutamine echo stress tests submitted by single institutions ranged from 70% to 80%, indicating similar interpretability of stress echocardiograms (Figure 6).

Agreement depending on image quality. Image quality had a significant effect on the overall agreement on presence or absence of inducible wall motion abnormalities. In the 13 patients whom dobutamine stress echo tests were recorded with highest image quality (grade A, allowing good delineation of all left ventricular wall segments) agreement on the presence or absence of inducible wall motion abnormalities was 100% on a 4/5 or 5/5 basis. However, for the 14 patients with the lowest image quality (grade E) agreement was only 43% significantly less than for those having the highest images quality (p=0.003) (Figure 7).

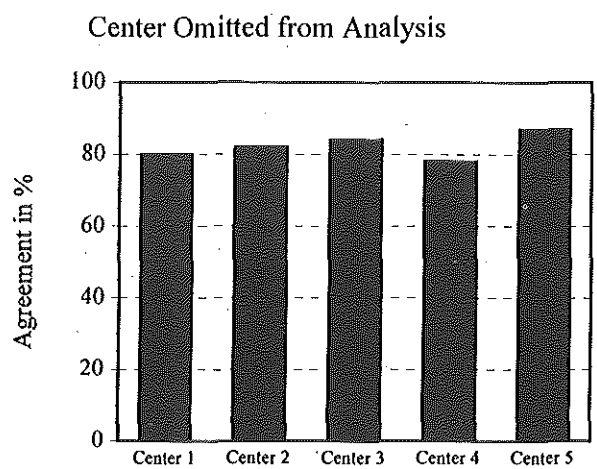


Figure 5 - Majority interinstitutional agreement on a three of four or four of four basis for positivity or negativity of dobutamine stress echocardiographic results when one instution is omitted from the analisy.

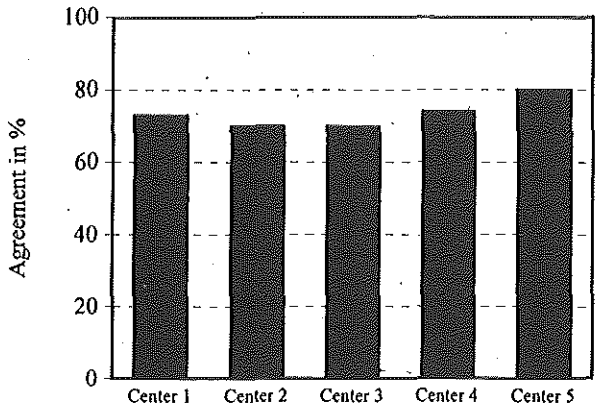


Figure 6 - Majority interinstitutional agreement on dobutamine stress echocardiographic test results (n = 30) submitted by each institution.

While none of the patients were excluded from the full analysis due to poor image quality, if patients with E-quality images were omitted, the interinstitutional agreement increased to 77%.

Agreement related to the images recording system. Agreement on a 4/5 or 5/5 basis for those 82 dobutamine echo-stress tests recorded on video-tape format was 71%.

This was similar to the 76% agreement in 68 studies recorded on video-tape after digital image processing.

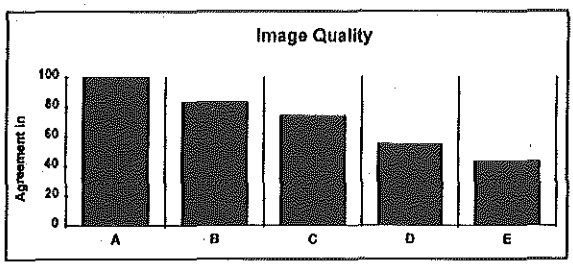


Image Quality	A	B	C	D	E
Agreement	100%	83%	74%	55%	43%
Number of patients	13	47	35	41	14

Figure 7 - Majority interinstitutional agreement by assessment image quality of dobutamine stress echocardiograms.

Discussion

Variability in test interpretation. Interobserver variability is a well known problem in cardiology and almost all diagnostic methods have been examined for inter and intraobserver agreement.

A surprisingly low level of interobserver agreement has been reported for interpretation of resting 12-lead ECG.

In a study of 20 physicians who were asked to interpret 100 ECGs as normal showing an old myocardial infarction or showing non specific abnormalities, Segall et al. (5) found 70% or more of the readers agree on only 77% of the studies. A similar interobserver difference has been reported in the frequency of "abnormal" exercise ECG diagnosis (6). Blackburn (7) asked 14 readers from 7 institutions to interpret 38 exercise ECG tests as normal, abnormal or borderline and found that abnormality was identify in 5-58% of studies. The results of imaging studies are also prone to interobserver variability. Atwood et al. (8) assessed the agreement of four experienced readers in the interpretation of 100 thallium perfusion images. The interobserver agreement for a majority of observers (three or four of four observers) from the same institutions was found to be 75% for an abnormal and 68% for a normal interpretation. A striking interobserver variability has been reported in the interpretation of coronary stenosis severity and left ventricular function evaluation at coronary angiography. Zir et al. (9) found that in only 13 of 20 coronary angiograms (65%) did all 4 experienced coronary angiographer (from the same institution) concur regarding the significance of stenosis (defined as $\geq$ 50% diameter luminal narrowing). De Rouen et al (10) et al. reported a 31% overall disagreement between the assessment of single readers and those of an expert panel on the classification of a coronary vessel as $\geq$ 70% stenotic. For left ventriculograms, the average percent disagreement in interpretation of wall motion between observers dividing the ventricle into five segments was 42%. The agreement on left ventricular contraction grade assessment was found to be only fair, with an average coefficient of agreement (kappa) of 0.34 among 11 readers (10).

Like most techniques in medicine, dobutamine stress echocardiography requires observer interpretation and is thus subjective to same extent. Several groups have reported their interobserver variabilities to both evaluate the degree of consistency in the interpretation of stress echocardiograms and to measure for interpretations validity. Sawada et al. (1) reported agreement between two observers of the same institution on the presence or absence of a stress-induced abnormality in 91% of cases, and Beleslin et al. (13) reported an interobserver agreement between two observers of 93%.

A high degree of correlation between wall motion score indexes evaluated by two different observers has also been reported before as well as after dynamic stress during exercise echocardiography (11). However, the evaluation of wall motion score as a global measurement does not allow a statement on agreement of specific left ventricular segments, and has only limited value for assessment of specific regions. Moreover, these studies of interobserver variability have focused on observers from the same institution with all observers frequently participating in joint stress echo reading sessions.

Sources of interobserver variability. The reasons for interobserver variability in stress echocardiography may be classified into three broad categories: 1) normal regional variability of left ventricular function in response to dobutamine stress; 2) variability of image quality; 3) variability of stress echocardiography hardware, in particular image storage on video tape or in digitized format; and 4) observer variability. The normal human left ventricular functional response to dobutamine stress is characterized by substantial regional variability whithin each patient, as shown by studies with cine-computer tomography (14), magnetic resonance imaging (15) and two-dimensional echocardiography (16). This heterogeneity of left ventricular wall thickening can be magnified by dobutamine infusion even in subjects without coronary artery disease, and there may be ambiguity with respect to differentiating this normal variation from the presence of disease.

To obtain a high degree of interobserver agreement, multiple views are necessary to visualise all segments of the left ventricle with high quality images.

Competence of the observer in the interpretation of stress echocardiograms is essential to reach high accuracy and thus a high interobserver agreement. This has been stressed by Picano et al. (17), who found accuracy in the interpretation of stress echocardiograms to be significantly higher for echocardiographers with a high level of experience with stress echocardiography. However, for a high interobserver agreement, there also needs to be homogeneity in the classification of a wall motion as being normal, hypokinetic, akinetic or dyskinetic. This applies especially to the classification of hypokinetic wall motion which may ranges from slight to severe and were the cut-off from what is considered normal may vary between observers and institutions. Mild hypokinesia may be viewed as normal clinical variability at one institution and be considered pathologic at another.

Significance of this study. To our knowledge, the present study is the first to analyse interobserver agreement among experienced stress echocardiographers from different institutions. There was consider-

able discrepancy between centers in their evaluation of dobutamine stress echocardiograms.

The number of studies evaluated as positive ranged from 38 to 102 between the five centers. This is reflected by an average coefficient of agreement (kappa) of 0.37 which is only fair. The fact that one center found significantly higher rates of dobutamine echocardiographic positivity than others indicates a systematic difference in reading criteria, implying different "threshold" at different places to classify stress echocardiographic results as positive or negative. This stresses the necessity to further refine and unify reading criteria.

Interobserver agreement was significantly influenced by echocardiographic images quality, with higher agreement in patients with high image quality then in those with limited image quality. Although no patients was excluded due to low echo image quality improvement in interobserver image agreement could have been obtained by excluding the 10% of patients with lowest image quality. These findings suggest that it is reasonable to exclude patients from stress echocardiography if image quality is insufficient to visualize all left ventricular segments.

Segmental agreement was found to be highest for the anterobasal and lowest for the inferobasal region. This might be due to the lower endocardial border definition in the inferobasal region in many patients and reduced wall thickening present at baseline compared with other left ventricular segments. Reduced accuracy in the detection of inducible wall motion abnormalities for this area has been reported previously (18).

Although we did not show better concordance on the basis of digitized image loops compared with videotaped recordings, the present study design may have placed the digital approach at a disadvantage, because recording digitized data on video-tape is associated with a slight decrement in image resolution, and this approach limits the ability to use stop-frame images, which facilitate interpretation. Although digitized cine loop displays are desirable to simplify analysis, the place of digital image processing for dobutamine echocardiography is unresolved, with data supporting (19) as well as disproving (20) improvement in accuracy by application of this technique.

Ideally, compatibility of different digitizing systems would permit digitized images to be readable by all systems independent of the system acquiring the images. Furthermore, it is desirable that the digitized segment of the original echocardiogragic screen displays the left ventricle with maximal spatial resolution.

The problem of considerable interobserver variability has been reduced for other imaging techniques. Computer-assisted quantitative

coronary angiography has diminished variability in interpretation of coronary angiograms. The agreement in interpretation of planar thallium-201 imaging as having ischemia or no ischemia could be increased from kappa value of 0.36 without standardization on interpretation to 0.71 with standardization of display and quantification (21). Similar improvements should be the goal with stress echocardiography. In the future, improved image quality allowing better endocardial border definition, possibly obtainable by left heart contrast echocardiography or computer algorithms to evaluate wall motion abnormalities, may diminish the subjective nature of interpretation and reduce the interobserver variability.

Limitations of the study. Quantitative coronary angiography was not performed in the present study. However, this was not thought to be inadequate because the main purpose of the study was to determine agreement in interpretation of stress echocardiograms, and the issue of correlation between dobutamine stress echocardiography and angiography has been repeatedly analyzed in previous studies.

In the present study, data acquisition as well as equipment were heterogeneous, with videotaped recordings in 82 patients and digital image storage in 68 patients. Video tapes were used as the final uniform media because different image acquisition and display system were implemented at the different centers. Furthermore, in 32 patients only apical views were available for evaluation.

No standardardization of stress echocardiographic reading criteria was defined. These criteria were clearly heterogeneous between centers, with aggressive, liberal "overreaders" as well as conservative "underreaders". We did nothing to prevent these disparate reading policies because the documentation of these variation was part of the rationale of the study. The results describe the current heterogeneity of these criteria among expert groups.

Interinstitutional agreement was found to be dependent on the severity of the coronary artery disease. Thus, agreement might have one- or two-vessel coronary artery disease because this was the group with the greatest disagreement.

Conclusions and clinical implications. A high intercenter agreement on the interpretation of test results is important for clinical decision making. The present study shows that the current heterogeneity in data acquisition and reading criteria between different centers result in relatively low interinstitutional agreement in the interpretation of stress echocardiograms between different institutions, additional efforts toward standardisation and communication are needed.

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CHAPTER IV

CORRELATION OF CORONARY STENOSIS BY QUANTITATIVE CORONARY ARTERIOGRAPHY WITH EXERCISE ECHOCARDIOGRAPHY*

Several studies have been addressed to assess the value of exercise echocardiography to predict the presence of "significant" coronary artery disease (1-7). However, a standardized definition of the gold standard for "significant" coronary artery obstruction is lacking. The classification of coronary artery disease in the literature on stress echocardiography is mostly semiquantitative by visual assessment (1,2,5-7) and in the few reports with a quantitative assessment of coronary angiography different angiographic parameters and different cut-off values for each parameter were considered (8-10). To contribute to clarify this issue, we studied with exercise echocardiography and quantitative coronary arteriography a selected population with no previous myocardial infarction, normal electrocardiogram and echocardiogram at rest, and a proximal single site single vessel coronary obstruction from mild to severe. The specific aim of the study was to assess the value of the obstruction severity to predict a positive exercise stress test, where the end points of angina, ST segment depression and new wall motion abnormalities were separately analyzed.

The study population consisted of 34 patients (27 men, 7 women, mean age 59±11 years, range 32-78) who performed exercise echocardiography at our Institution. Inclusion criteria were: 1) no previous myocardial infarction or previous cardiac surgery; 2) normal wall motion at baseline echocardiogram; 3) normal electrocardiogram at rest; 4) coronary stenosis limited to one major artery at coronary arteriography performed within one week of exercise echocardiography. Patients with unstable angina were excluded. Reasons to perform exercise echocardiography were the evaluation of chest pain in 26 patients, while the other 8 were part of an ongoing study on restenosis after percutaneous transluminal coronary angioplasty which included coronary arteriography at 6-month fol-

* Salustri A, Arnese M, Boersma E, Cornel JH, Baptista A, Ten Cate FJ, de Feijter, Roelandt JRTC, Fioretti PM. Am J Cardiol 1995; 75:287-290.

low up. All the antianginal medications, including betablockers, were withdrawn before the exercise test.

Symptom limited upright bicycle ergometry was performed with stepwise increments of 20 Watts each minute. Electrocardiogram was continuously monitored (lead II, V2, V5) and 12-lead electrocardiogram was recorded at rest and every minute throughout the test. Cuff blood pressure was measured at rest and every 2 minutes. The electrocardiographic complexes were analysed by a computer-assisted system (Cardiovit CSG/12, Schiller), and a horizontal or downsloping ST segment depression $\geq$1 mm occurring 80 msec after the J point was considered as ischemic.

Two-dimensional echocardiograms were performed with a commercially available wide angle phased array imaging system equipped with either a 2.5 or 3.5 MHz transducer. Images of standard views were obtained at rest and immediately after exercise with the patients lying in the same left lateral decubitus. The last post-exercise images were acquired within 90 seconds from the termination of exercise test. Both rest and stress images were digitized on-line and stored for subsequent analysis on cineloop display.

All echocardiograms were analysed and a consensus was achieved by two observers without knowledge of clinical data, exercise electrocardiographic and angiographic results. Left ventricular wall motion was evaluated on a 16-segment, 4-grade scale model. The development of wall motion abnormality after stress was considered as an ischemic response. The location of wall motion abnormalities was related to the different coronary arteries as previously described by Broderick et al (11). The low level of inter- and intraobserver variability obtained in our laboratory for the interpretation of exercise echocardiography has been previously reported (12).

All the patients underwent coronary arteriography with the Judkins technique. Coronary arteriograms were reviewed using the Cardiovascular Angiography Analysis System (Pie Medical, The Netherlands) with authmatic luminal edges detection. This system has been described and validated earlier (13). All measurements were performed in end-diastolic frames with optimal vessel opacification.

Data are expressed as mean $\pm$ standard deviation. The unpaired Student's t test was used to compare percent diameter stenosis and minimal lumen diameter in patients with and without a positive exercise echocardiogram. Receiver Operator Characteristic curves analysis was used to display the sensitivity and specificity of the percent diameter stenosis and the minimal lumen diameter during the whole range of measurements for the prediction of an ischemic response during exercise stress test. From these curves, the optimal cut-off was chosen as the point of interception between sensitivity and specificity of each angiographic variable.

The mean peak heart rate and the double product were 148±23 b/min and 28066±5480, respectively. Angina occurred in 8, ST segment depression in 16, and new wall motion abnormalities in 14 patients. The location of wall motion abnormalities was always consistent with the site of the coronary obstruction. Twenty-seven patients reached the 85% of the maximal age and sex predicted heart rate. In the 3 patients with a negative exercise echocardiogram who did not reach the 85% of maximal age and sex predicted heart rate, the test was interrupted for ST segment depression in 2 and angina in 1.

Seventeen patients had a lesion of the left anterior descending artery, 5 had a left circumflex disease and 12 a right coronary disease. The distribution of the lesions severities in the entire population is displayed in figure 1. Significant differences between patients with positive and negative exercise echocardiography were found for both quantitative angiographic measures (62% vs 41%, p<0.0001, and 0.88 vs 1.51 mm, p<0.0001).

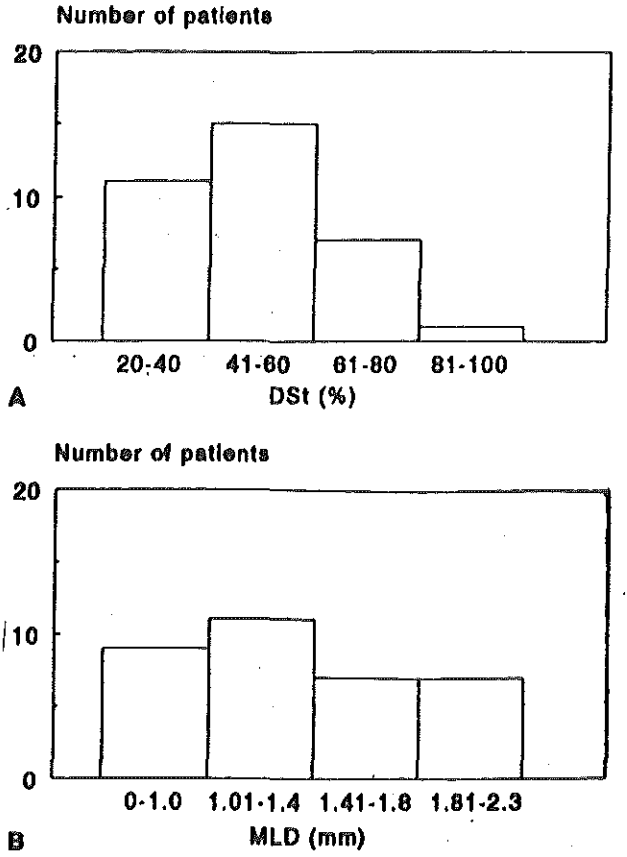

Figure 1 - Distribution of coronary lesion severities in the study group evoluated by percent diameter stenosis (DSt) (A) and minimal lumen diameter (MLD) (B).

Sensitivity and specificity of the individual values of percent diameter stenosis and the minimal lumen diameter for the correct classification of patients with and without exercise induced ischemia is depicted in figure 2 and 3. The "best" cut-off point for predicting wall motion abnormalities during exercise (defined as the value of diameter stenosis at the cross-point of sensitivity-specificity curves) was 52% (figure 2A), yielding a sensitivity and specificity of 74%. In

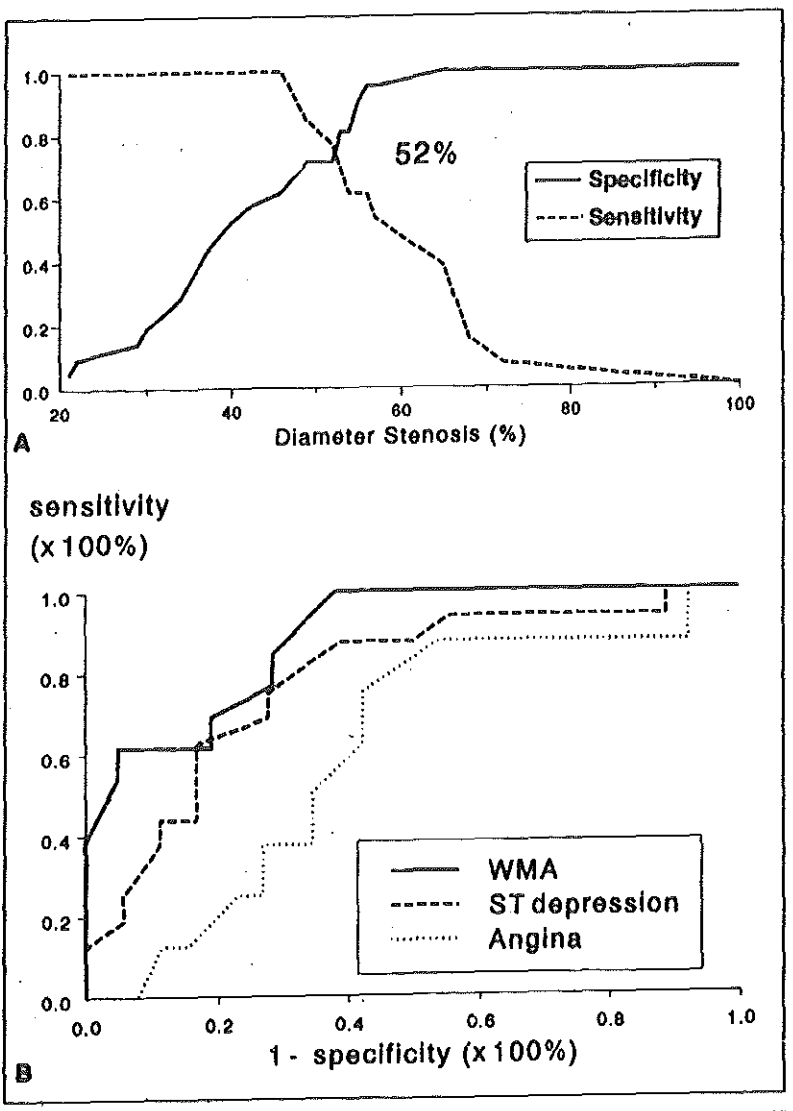

Figure 2 - A, percent correct classification of presence (sensitivity) or absence (specificity) of exercise-induced wall motion abnormalities as a function of the whole spectrum of percent diameter stenosis. B, receiver-operator characteristic curves for comparison of the diagnistic accuracy of percent diameter stenosis for the different markes of myocardial ischemia during bicycle ergometry. WMA = new wall motion abnormalities.

figure 2B, the Receiver Operator Characteristic curves of angina, ST segment and wall motion abnormalities are separately represented. Since the sensitivity/specificity curve for wall motion abnormalities is the highest, the severity of the percent diameter stenosis is better related to the mechanical ischemic marker from echocardiography than angina and ST depression.

In figure 3, the merit of minimal lumen diameter is displayed in the same way, confirming the superiority of wall motion abnormalities,

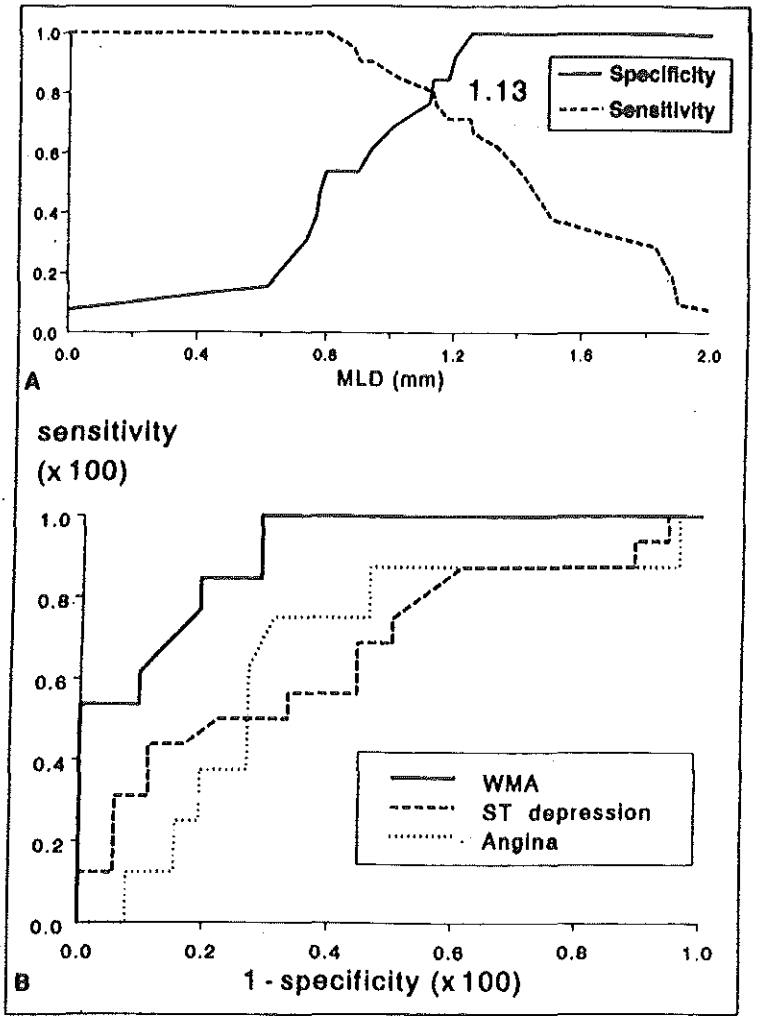

Figure 3 - A, percent correct classification of presence (sensitivity) o absence (specificity) of exercise-induced wall motion abnormalities as a function of the whole spectrum of minimal lumen diameter (MLD). B, receiver-operator characteristic curves for comparison of the diagnostic accuracy of minimal lumen diameter for the different markes of myocardial ischemia during bicycle exercise. WMA = new wall motion abnormalities.

in comparison to angina and ST segment depression. The "best" cut-off point for the prediction of wall motion abnormalities was 1.13 mm (sensitivity and specificity of 83%).

The predictive values of minimal lumen diameter and the percent diameter stenosis for new wall motion abnormalities were similar, since the areas below the respective Receiver Operator Characteristic curves were not statistically different (8864 vs 9121).

Our study includes a well defined group of patients with single vessel disease, a proximal single site obstruction, a wide range of stenosis severity (from 21 to 100%), with a balanced prevalence of exercise induced wall motion abnormalities. Furthermore, we avoided the confounding effect of wall motion abnormalities at rest, abnormal baseline electrocardiogram, and β-blocker therapy. The main findings of the present study can be summarized as follows:

1. in patients with mild to severe obstruction of a single vessel, a minimal lumen diameter of 1.13 mm and a percent diameter stenosis of 52% are the cut-offs which best differenciate patients with and without new wall motion abnormalities on post-exercise echocardiogram;

2. sensitivities and specificities of these cut-off points are similar, suggesting that minimal lumen diameter and percent diameter stenosis have similar predictive accuracy for exercise induced wall motion abnormalities;

3. the severity of coronary obstruction is poorly related to ST-segment depression and angina during exercise.

From the curves displayed in figures 2A and 3A we selected the cross-point of sensitivity and specificity curves as the "optimal" cut-off. However, using another decision rule (as for instance an utility function where sensitive test would be more appropriate) different cut-off points can be defined and the corresponding sensitivity/specificity values derived. This allows the immediate evaluation of reciprocal changes of sensitivity and specificity values over the whole range of cut-off values.

Quantitative analysis of coronary arteriography has been correlated to exercise echocardiography by Sheikh et al (9) and Agati et al (10). The results of the study from Sheikh et al (9) (who evaluated 34 patients, 18 of which had an ischemic response on echocardiogram) indicate that the positivity of exercise echocardiogram is directly related to the severity of the coronary obstruction. However, the value of exercise induced angina and ST segment changes was not compared to new wall motion abnormalities. The optimal cut-off points of quantitative coronary angiography were not calculated directly by the authors. From the raw data of all the individual patients, we generated sensitivity-specificity curves for percent diameter stenosis and minimal

lumen diameter, yielding relative cut-off points of 53% and 1.2 mm, similar to our study. The sensitivity/specificity values at their cross-point were 94 and 85% respectively.

The data from Agati et al (10) apparently differ from ours, since they found that exercise echocardiography could best differenciate patients with a more severe coronary obstruction, by a diameter stenosis $\geq$ 85% and a minimal lumen diameter $\leq$ 0.7 mm. This discrepancy is probably due to the different study group (only few patients at the lower end of the range of lesion severity), different type of exercise test (supine bicycle with imaging at peak stress), and different criteria for the positivity of the echocardiogram based on the quantitative assessment of segmental area shortening.

The comparison of the present findings with those from a previous study on dobutamine stress echocardiography (14) is interesting. In that study, the "best" cut-off for the obstruction severity was defined as the point of maximal sum of sensitivity and specificity, when the sensitivity was equal or greater than the specificity, yielding a value of 52% for diameter stenosis and 1.07 mm for minimal lumen diameter. Using the same approach as in the present study (the point of interception), the angiographic cut-off values were 54% (sensitivity and specificity 78%) and 1.0 mm (sensitivity and specificity 76%), respectively. These results are very consistent with those found in the present study with post-exercise echocardiography. They strongly suggest that high dose dobutamine-atropine stress echocardiography, an exercise simulating but not physiologic test, performs equally well for determining the functional consequences of coronary obstructions in the major epicardial coronary vessels.

In conclusions, the severity of a coronary lesion evaluated by quantitative coronary arteriography can predict an ischemic response on exercise testing. Among the different ischemic markers, wall motion abnormalities are better predicted than S-T segment changes or angina.

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CHAPTER V

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS OF ISOLATED LEFT ANTERIOR DESCENDING CORONARY ARTERY STENOSIS: CORRELATION WITH EXERCISE ECHOCARDIOGRAPHY AND 99m-Tc MIBI SPECT*

Abstract

Objectives. The aim of this study was to assess the value of quantitative coronary arteriography to predict an ischemic response at exercise echocardiography and MIBI single photon emission computed tomography (SPECT) in patients with single vessel disease of the left anterior descending (LAD) coronary artery.

Background. The relation between the severity of coronary stenosis and the ischemic response of exercise echocardiography and perfusion scintigraphy in patients with single vessel LAD disease is not well established.

Methods. Thirty-one patients without previous myocardial infarction and with isolated stenosis of different degree in the proximal or mid portion of LAD were studied. Quantitative arteriographic analysis was used for measurements of percent diameter stenosis (DS) and minimal lumen diameter (MLD). Exercise induced wall motion abnormalities by echocardiography and transient perfusion defects by MIBI SPECT were considered as a positive response. The analysis of sensitivity/specificity curves and Receiver Operator Characteristic curves was applied to establish the diagnostic power of quantitative coronary arteriography (DS and MLD) to predict an ischemic response at exercise echocardiography and MIBI SPECT.

Results. The "best" angiographic cut-off values to predict a positive exercise echocardiography and scintigraphy were similar (DS of 52% and MLD of 1.12 mm for echocardiography; DS of 49% and MLD of 1.20 mm for SPECT). However, the sensitivity/specificity at cross point was slightly higher (even if not statistically significant) for echocardiography than SPECT, both for DS (81% vs 67%) and MLD (81% vs 74%), suggesting a closer relation of quantitative coronary

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arteriography with the outcome of echocardiographic than scintigraphic exercise testing.

Conclusions. The functional significance of a proximal/mid LAD coronary artery stenosis measured with quantitative coronary arteriography is slightly better related to echocardiographic than scintigraphic markers of exercise induced myocardial ischemia.

Introduction

Anatomic information derived from arteriography is not always predictive of the physiologic significance of a coronary stenosis (1). Several noninvasive techniques have been proposed to assess the functional significance of a coronary stenosis detected by contrast arteriography. Exercise testing in conjunction with echocardiography (2-4) or perfusion scintigraphy (5,6) has been extensively used for the evaluation of patients with suspected or known coronary artery disease and data available on the comparative value of the two methods in the same population demonstrate that they have similar diagnostic accuracy (7-12). However, in these previous studies coronary arteriography was not quantitatively evaluated, and the confounding effects of previous myocardial infarction and abnormal wall motion at rest were not always avoided.

Accordingly, we wanted to investigate which quantitative angiographic parameter best correlates with exercise-induced wall motion abnormalities and with transient perfusion defects. For this aim, a selected population with proximal or mid left anterior descending (LAD) coronary artery stenosis and no previous myocardial infarction was studied and Receiver Operator Characteristic (ROC) curves analysis was used as an objective method for determining the power of quantitative angiographic parameters for the prediction of an abnormal exercise echocardiogram and SPECT.

Methods

We selected 31 consecutive patients (23 males, mean age 57±11 years, range 32 to 78) referred for the evaluation of chest pain or enrolled in follow-up studies after percutaneous coronary angioplasty who fulfilled the following inclusion criteria: 1) proximal or mid LAD coronary artery stenosis at arteriography judged from mild to severe by visual assessment; 2) no history of previous myocardial infarction; 3) simultaneous exercise echocardiography and MIBI SPECT performed within 2 weeks from coronary arteriography; 4) normal wall motion and perfusion at rest. Patients with unstable angina were excluded.

Exercise testing procedure. Symptom-limited upright bicycle ergometry was performed with stepwise increments of 20 Watts each minute. Electrocardiogram (ECG) was continuously monitored (lead II, V2, V5) and 12-lead ECG was recorded at rest and every minute throughout the test. Cuff blood pressure was measured at rest and every two minutes. The ECG was analysed by a computer-assisted system (Cardiovit CSG/12, Schiller), and a horizontal or downsloping ST segment depression >1 mm occurring 80 msec after the J point was considered as ischemic.

Exercise echocardiography. Two-dimensional echocardiograms were performed with a wide-angle phased-array system equipped with either a 2.5 or 3.5 MHz transducer. Resting images were acquired in the standard views (parasternal long- and short-axis, apical 4- and 2-chamber), with the patients in the left lateral decubitus. Post-exercise images were obtained immediately after the termination of exercise testing, with the patients lying in the same rest position. The first stress images were always acquired within 1 minute from the termination of exercise.

Both rest and stress images were recorded on video tape, digitized on-line and stored for subsequent analysis.

Analysis of exercise echocardiography. Rest and exercise digitized two-dimensional images were reviewed on a side-by-side cine-loop display and video tape. Images were interpreted by two experienced investigators who were blinded to the patient's clinical data, exercise ECG and angiographic results. Agreement between the two observers was required for the classification of the wall motion abnormalities. In case of disagreement, the opinion of a third investigator was binding. For purpose of analysis, left ventricular wall motion was evaluated on a 16-segment model, each segment being scored using a 4-point scale, where 1=normal wall motion and thickening, 2=hypokinesis, 3=akinesis (absence of systolic wall motion and thickening), and 4=dyskinesis (systolic outward wall motion with thinning). An ischemic response was defined as an exercise-induced wall motion abnormality. The low level of inter- and intra-observer variability obtained in our laboratory for the interpretation of exercise echocardiography has been previously reported (8). The location of the wall motion abnormalities was correlated with coronary arterial distribution by using the methodology described by Segar et al (13).

Exercise MIBI SPECT. About one minute before the termination of the exercise stress test, 370 MBq of 99-m technetium MIBI were injected in an antecubital vein through a previously inserted cannula. Stress SPECT images were acquired one hour after injection. A resting MIBI SPECT was performed on a separate day, one hour after a new injection of the same dose of radiotracer.

Analysis of SPECT. For each patient, six short-axis slices and 3 vertical long-axis slices were displayed and analysed. As previously described (14), the left ventricle was divided in 47 segments and each segment was scored on a 4-point scale (from 1=normal to 4= "absence" of uptake). The visual analysis was performed by two observers with the assistance of the circumferential profile analysis of the short-axis slices. The apical portion was assessed only visually on the vertical and horizontal long-axis slices. An ischemic response was based on the presence of transient perfusion defect.

Quantitative coronary arteriography. All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, the Netherlands). The automated edge detection of the system has been validated and described elsewhere (15). A region of interest of 512x512 pixels was selected and digitized using a high-fidelity charge coupled device camera. The luminal edges were detected on the basis of a weighted sum of the first and second derivative function of the brightness profile of each scanline perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using the catheter tip as a scaling device. A computer derived estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated reference diameter. This technique is based on a computer-derived estimation of the original values over the analyzed region. The calculation is based on a first degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment followed by a translation to the 80th centile level. All measurements were performed from end-diastolic frames with optimal vessel opacification.

Statistical analysis. All continuous variables are expressed as mean ± SD. The agreement between echocardiography and SPECT was defined as the percentage of concordant diagnosis and it was also assessed by calculating the kappa (k) value and the corresponding 95% confidence intervals (C.I.). Receiver Operator Characteristic curves analysis was used as an objective method for determining the power of the angiographic parameters (DS, MLD) for the prediction of an abnormal exercise echocardiography and SPECT. The sensitivity and specificity were plotted against the whole range of measurements of a specific parameter for determining the "best" cut-off point. The best cut-off point was defined as the intersection of the sensitivity/ specificity curves. The sensitivity/specificity values at these cut-off points are reported as percent with the corresponding 95% C.I.

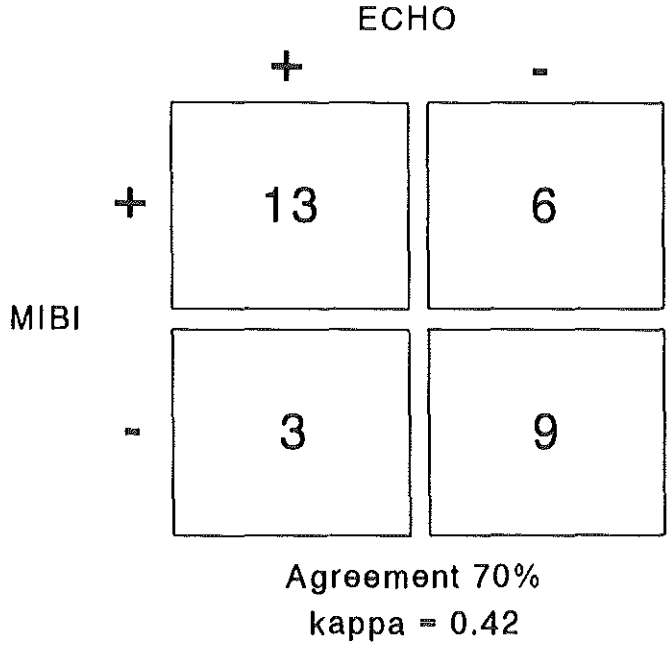

Figure 1 - Two-by-two table for the agreement of an ischemic response by exercise echocardiography (ECHO) and MIBI SPECT.
+ = positive response; - = negative response.

Results

Exercise testing results. The mean maximal heart rate was 145 beats/min (range 120-190). The 85% of the maximal age-predicted heart rate was not reached in 8 patients. In 4 cases the exercise was stopped because of chest pain, and in the other 4 for fatigue (in 3 of these last 4, echocardiography was positive). During the exercise test, angina occurred in 9 patients and ST segment depression (horizontal or downsloping > 1 mm) in 14.

Exercise echocardiography. New wall motion abnormalities were detected on post exercise echocardiogram in 16 patients. The site of wall motion abnormalities was always consistent with the territory of LAD.

Exercise SPECT results. Transient perfusion defects were present, all in the distribution territory of the LAD, in 19 patients. The agreement between echocardiography and SPECT for the diagnosis of myocardial ischemia is represented in figure 1 (22/31=70%, kappa value = 0.42, 95% C.I. 0.10-0.74). Of the 9 patients with discordant responses, 6 had positive SPECT and negative echocardiograms. The median DS and MLD in these 6 patients were 35% (range 30-53%) and 1.89 mm (range 1.12-2.26 mm), respectively.

Quantitative arteriography and exercise-induced myocardial ischemia. Quantitative coronary arteriography revealed a mean percent DS of 52±19 (range 30% to 100% - 2 patients with total occlusion). The DS was <50% in 14 patients, 50 to 70% in 13, and >70% in 4. The mean MLD was 1.20±0.58 mm (range 0 to 2.26 mm). Faint collaterals were visible in the 2 patients with occluded artery.

Sensitivity and specificity of the individual values of DS and MLD for the correct classification of patients with and without exercise-

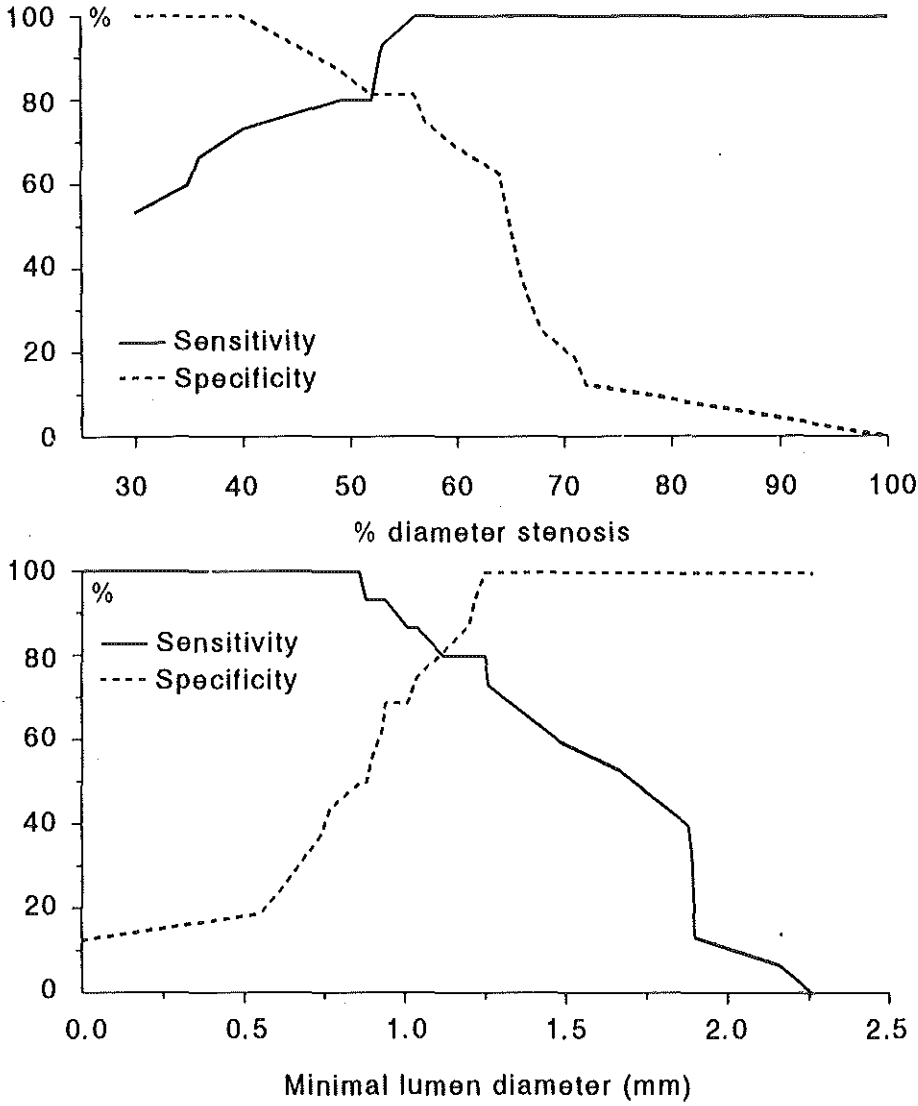

Figure 2 - Percentage correct classification of presence (sensitivity) or absence (specificity) of exercise induced wall motion abnormalities as a function of cut-off points over the whole spectrum of percent diameter stenosis (panel A) and minimal lumen diameter (panel B).

induced myocardial ischemia are depicted in figure 2 (panel A and B) for echocardiography and in figure 3 (panel A and B) for SPECT. From these figures it can be observed that the "best" cut-off point of DS (defined as the value at the cross-point of sensitivity and specificity curves) for predicting a positive response during exercise was similar for echocardiography and SPECT (52% vs 49%, respectively). However, the sensitivity/specificity cross-point was slightly higher

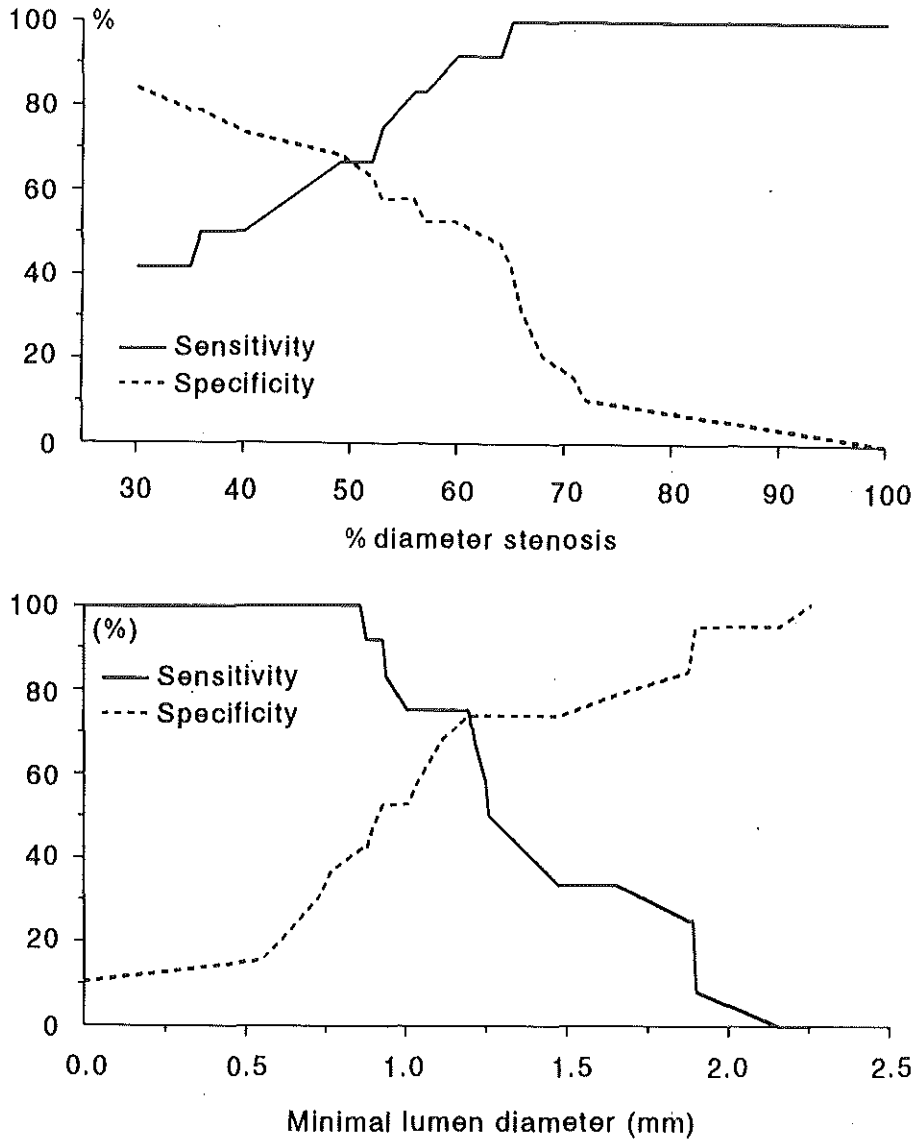

Figure 3 - Percentage correct classification of presence (sensitivity) or absence (specificity) of transient perfusion defects as a function of cut-off points over the whole spectrum of percent diameter stenois (panel A) and minimal lumen diameter (panel B).

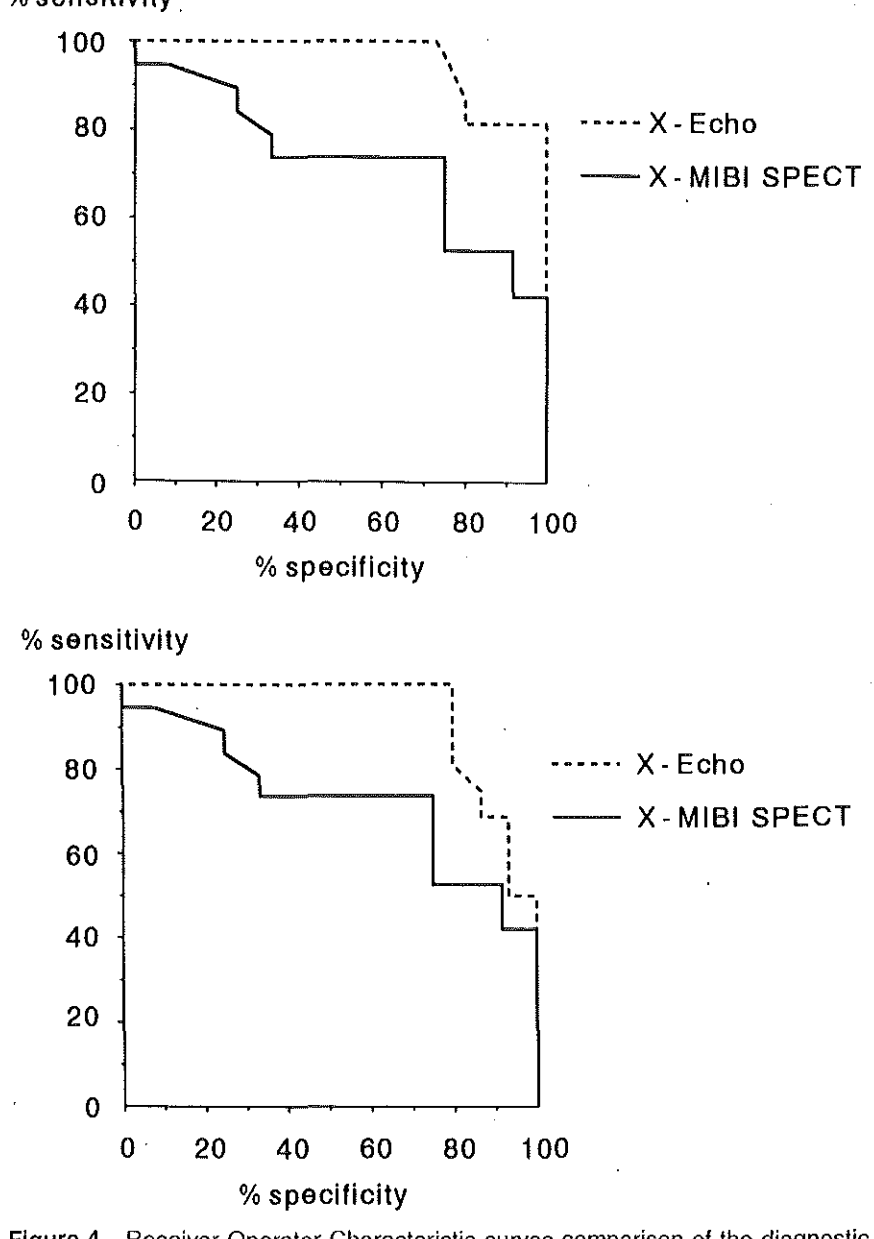

Figure 4 - Receiver Operator Characteristic curves comparison of the diagnostic accuracy of percent diameter stenosis (panel A) and minimal lumen diameter (panel B) for the prediction of wall motion abnormalities and transient perfusion defects during bicycle ergometry.
For percent diameter stenosis, the ares below the ROC curves (expressed as percent of the maximal theoretical area, and 95% confidence intervals) are 95 (89-100) for echocardiography and 74 (57-91) for SPECT. For minimal lumen diameter, the corresponding values are 93 (84-100) and 73 (55-90), respectively.
X-Echo = exercise echocardiography; X-MIBI SPECT = exercise SPECT.

for echocardiography than SPECT (81%, 95% C.I 54-96, vs 67%, 95% C.I. 43-87). Similar results were found considering the MLD, including a similar "optimal" cut-off (1.12 mm vs 1.20 mm) and a trend suggesting a slightly higher sensitivity/specificity cross-point for exercise echocardiography (81%, 95% C.I. 54-96, vs 74%, 95% C.I. 48-90).

In figure 4, the ROC curves of quantitative coronary arteriography for the prediction of wall motion abnormalities and perfusion defects are separately represented. There is a clear trend showing that the areas below the ROC curves for the prediction of new wall motion abnormalities were larger compared to those for the prediction of transient perfusion defects. This observation suggests that these angiographic parameters are better related to the mechanical than to the perfusion marker of ischemia.

The accuracy of DS and MLD for new wall motion abnormalities was similar, since the areas below the respective ROC curves were not statistically different (93% vs 95%).

Discussion

Although coronary artery disease comprises a continuous spectrum of obstruction severities, the diagnostic accuracy of noninvasive tests mostly relies on one arbitrary angiographic cut-off value to define "significant" disease. This "fuzzy" decision implies that some stenoses which are physiologically non significant may be included in the definition of the presence of disease, and also that some physiologically significant stenoses may be classified as non significant. Clearly, this is a crucial issue since one of the most important determinants of the sensitivity and specificity of noninvasive tests for the diagnosis of coronary artery disease is the definition of the angiographic reference (which parameter and which cut-off value for each parameter). In addition, many reports do not rely on quantitative angiographic assessment of coronary stenoses, which can be a major drawback of any study aiming at assessing the accuracy of any test for the diagnosis of coronary artery disease (1,16).

The present study. The aim of the present study was to assess the value of quantitative coronary arteriography to predict an ischemic response at exercise echocardiography and MIBI SPECT in a selected group of patients without previous myocardial infarction and isolated discrete mild to severe lesion in the proximal or mid-portion of the LAD coronary artery. To address this problem, quantitative measurements of the coronary stenoses were performed by quantitative coronary angiography, and the functional end-point of the study was the ischemic response on symptom limited exercise echocardiography

and MIBI SPECT, which were simultaneously applied in all patients. To assess the relationship between coronary stenosis and exercise induced ischemia over the whole range of obstruction severity, the ROC and the sensitivity/specificity curves from the percent DS and MLD were analyzed. This approach allows the identification of the most efficient angiographic cut-off values for predicting an ischemic response on stress echocardiography and SPECT. At this aim, we used an utility function where sensitivity and specificity are considered equally appropriate.

This study provides new information, since the few previous comparative studies between exercise echocardiography and perfusion scintigraphy (7-12) were confounded by the inclusion of patients with previous myocardial infarction or multivessel coronary disease. Further, no study included a homogeneous group with single vessel LAD disease, the functional significance of different degrees of stenoses severity was not explored, and in some studies the quantitative assessment of coronary angiograms was not appropriate.

The main findings of this study can be summarized as follows:

1) the best angiographic cut-off values from DS and MLD to predict an ischemic response by exercise echocardiography and MIBI SPECT are similar; 2) the accuracy of DS and MLD to predict the functional outcome of exercise stress testing is similar; 3) quantitative coronary arteriographic measurements are slightly better related to echocardiographic than to scintigraphic results.

The "best" angiographic variables and cut-off values. The diagnostic accuracy of DS and MLD was similar for the prediction of both exercise echocardiography and MIBI SPECT. This is in contrast to previous studies suggesting that MLD is a better parameter to characterize the functional significance of coronary stenoses (17). This difference maybe related to the patients selection. For instance, Wilson et al (18) found that, consistently with our results, DS is a functionally meaningful variable in patients with discrete single site coronary artery narrowing. It is likely that MLD is superior to DS for the functional assessment of the coronary obstruction in patients with a diffuse disease, which may be undetected or underestimated by measuring only the relative diameters differences (17,19). Consistent with our findings, recent data by Uren et al in patients with single vessel disease and normal left ventricular function have shown that myocardial blood flow during adenosine or dipyridamole induced hyperemia is equally well correlated with DS and MLD (inverse correlation with the percent of DS and direct correlation with the MLD) (20).

In the present study, the cut-off values which optimally separated patients with a normal from those with an ischemic response during exercise were defined as those corresponding to the cross-point of

the sensitivity/specificity curves (figures 2 and 3). They were 52% for DS and 1.12 mm for MLD, using the echocardiographic end-point. They were similar when MIBI SPECT was applied (49% and 1.20 mm, respectively). These results are in agreement with the cut-off values found applying a similar statistical approach, but utilizing different stress or imaging modalities like exercise ECG (21) or dobutamine echocardiography (22) as functional end-point.

Exercise echocardiography versus MIBI SPECT. An important finding of the present study is that the results of exercise echocardiography are predicted by quantitative coronary arteriography at least as well as those of MIBI SPECT. This can be concluded by the inspection of the ROC and the sensitivity/specificity curves. From the analysis of the ROC curves, the sensitivity and specificity for the prediction of a positive exercise echocardiogram are slightly higher than those for the prediction of a positive MIBI SPECT during the whole range of measurements of both DS and MLD (figure 4). This higher sensitivity and specificity of coronary angiography for the prediction of echocardiographic results is confirmed by the sensitivity/specificity curves (figures 2 and 3). The inspection of these curves allows the assessment of the sensitivity and specificity over the whole range of DS and MLD, and the cross-point represents the cut-off of the angiographic variables with the "optimal" sensitivity and specificity. In this specific case, it clearly appears that, while the values of both DS and MLD at the cross-point were similar for exercise echocardiography and MIBI SPECT, the sensitivity-specificity values at the cross point were slightly lower for MIBI SPECT than for echocardiography, implying a less strict relationship of coronary arteriographic measurements with scintigraphy than with echocardiography.

Several factors may explain the discrepancies between exercise echocardiography and MIBI SPECT. Both imaging methods have limitations and pitfalls. Perfusion SPECT may lack an optimal diagnostic accuracy for a variety of technical reasons, as soft tissue attenuation, overlying abdominal viscera, ventricular hypertrophy, cardiac rotation, patients motion (23). Acquisition of echocardiographic stress images is strongly operator dependent, and with the post-exercise acquisition some mild transient ischemia may be missed (24). Furthermore, SPECT perfusion imaging detects not only true myocardial ischemia but also malperfusion, which results in detection of stenosis of mild/moderate degree. This has been underscored in in recent observations by Uren et al in humans (20), who found a decline of the coronary vasodilator reserve during adenosine or dypiridamole induced hyperemia for moderate degree of coronary stenosis, starting from 40%, and an exaustion of coronary

reserve for stenoses greater than 80%. It is uncertain to establish which of these factors intrinsic to the two methods was of importance in our series. However, the results of the present study suggest that the "grey zone" for the prediction of exercise induced myocardial ischemia from quantitative coronary angiography is smaller for echocardiography compared to perfusion scintigraphy.

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CHAPTER VI

QUANTITATIVE CORONARY ANGIOGRAPHY IN THE ESTIMATION OF THE FUNCTIONAL SIGNIFICANCE OF A CORONARY STENOSIS. CORRELATIONS WITH DOBUTAMINE-ATROPINE STRESS TEST *

Abstract

Objectives: The purpose of this study was to determine the predictive value of quantitative coronary angiography in the assessment of the functional significance of coronary stenosis as judged from the development of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography.

Background: Coronary angiography is the reference method for assessment of the accuracy of non-invasive diagnostic imaging techniques to detect the presence of a significant coronary stenosis. However, use of arbitrary cut-off criteria for the interpretation of angiographic data may considerably influence the true diagnostic accuracy of the technique investigated.

Methods: Thirty four patients without previous myocardial infarction and with single coronary stenosis were studied with both quantitative angiography and dobutamine-atropine stress echocardiography. Two different techniques of quantitative angiographic analysis, edge detection and videodensitometry, were used for measurement of minimal lumen diameter, percent diameter and percent area stenosis. Two-dimensional echocardiographic images were collected during incremental doses of intravenous dobutamine and later analyzed using a 16 segment left ventricular model. Angiographic cut-off criteria were derived from receiver-operating curves to define functional significance of coronary stenosis based on dobutamine-atropine stress echo.

Results: The angiographic cut-off values with the best predictive value for the development of left ventricular wall motion abnormalities

* Baptista J, Arnese M, Roelandt JRTC, Fioretti PM, Keane D, Escaned J, Boersma E, Di Mario C, Serruys PW. J Am Coll Cardiol 1994;23:1434-9.

during dobutamine-atropine stress echocardiography were a minimal lumen diameter of 1.07 mm, a percent diameter stenosis of 52 %, and percent area stenosis of 75 %. Minimal lumen diameter was found to have the best predictive value of a positive dobutamine stress test (odds ratio 51, sensitivity 94% and specificity 75%).

Conclusions: Automated quantitative angiographic measurements of minimal luminal diameter is a practical and useful index for determining both the anatomical and the functional significance of a coronary stenosis and a value of 1.07 mm is the best predictor of a positive dobutamine stress test.

Introduction

Establishing the functional significance of a coronary stenosis detected by contrast angiography is a clinical challenge especially in the case of intermediate stenotic lesions. The traditional criteria for determining the presence of functionally significant disease, a 50 % reduction in lumen diameter by visual estimation, suffers from considerable inter- and intraobserver variability (1-3), making this criterion unreliable in the estimation of the functional impact of lumen obstructions (3). It is in the range of mild to moderate stenoses (30-60 % diameter stenosis) that the discrepancy between visual estimates and objective measurements of lumen dimensions is most marked (4, 5). Computerised quantitative coronary angiography reduces the latter source of error and provides objective measurements of lumen dimensions, but the physiological significance of a given coronary stenosis remains unclear. Because of the use of arbitrary cut-off criteria in previous studies addressing this problem, and in which coronary angiographic estimates of severity were compared with other imaging, objective indices are lacking.

Recently, dobutamine stress echocardiography has been introduced as a safe and reproducible technique for the diagnosis of coronary artery disease (6-13). Several studies have indicated a good correlation between the development of wall motion abnormalities during stress echocardiography and the severity of a coronary stenosis (6-15). However, these studies have limitations because either visual interpretation of the angiogram was performed (6,7,14) or arbitrary cut-off points (13) for quantitative angiographic data were used.

The goal of this study was to investigate which quantitative angiographic parameters of stenosis severity best correlates with the development of ischemia-induced wall motion abnormalities during dobutamine-atropine stress echocardiography. Angiographic cut-off criteria were derived from receiver-operating curves to obtain objective criteria for assessment of functional significance of stenosis severity.

Methods

Study Patients. The study patients included 34 consecutive patients referred from the catheterization laboratory, with a single coronary stenosis judged to have ³30% diameter stenosis by visual assessment. The coronary angiogram was performed within 2 weeks prior to the performance of dobutamine-atropine stress echocardiography. The stenosis was located in the left anterior descending coronary artery in 26 patients, left circumflex coronary artery in 3 patients, and right coronary artery in 5 patients. Mean age was 61.3 ±12.6 years (range 32 to 79). There were 21 (62%) men and 13 (38%) women. Patients with unstable angina, previous myocardial infarction, and left bundle branch block were excluded. Patients were under treatment with antianginal medication, consisting of beta-blocking agents (24 patients) either alone or in combination with nitrates and/or calcium-channel blocking agents, which was not discontinued prior to the study.

Dobutamine-atropine Stress Test. The protocol used at the Thoraxcenter in the performance of dobutamine-atropine stress echocardiography has been described in detail previously (16). Briefly, two dimensional precordial echocardiography was performed at rest and during incremental doses of dobutamine. After a baseline 12-lead electrocardiogram, dobutamine was infused through an antecubital vein starting at a dose of 10 μg/Kg/min for 3 minutes, and increasing by 10 μg/Kg/min every 3 minutes to a maximum of 40 μg/Kg/min (stage 4); this was continued for 6 minutes in the absence of an ischemic response. In patients not achieving 85% of maximal predicted heart rate, atropine (0.25 mg) was given intravenously at the end of stage 4, and repeated to a maximum of 1 mg with the continuation of dobutamine for a further 5 minutes if necessary to achieve the above mentioned target heart rate. The infusion of dobutamine was stopped if the patient developed marked new wall motion abnormalities, ST segment depression of >0.2 mV 80 ms after the J point, ST segment elevation, typical angina, significant arrhythmias, a decrease in systolic blood pressure > 40 mmHg from resting level, or any complication considered to be related to the stress test.

Standard apical and parasternal views were recorded in a closed cineloop in a quad-screen format, facilitating the comparison of rest and stress images, on super-VHS videotape. During the analysis of the images, the left ventricle was divided into 16 segments (17), each segment being scored using a 4 point scale: 1= normal wall motions and thickening; 2= hypokinesia; 3= akinesis (absence of systolic wall motion and thickening); 4= dyskinesis (systolic outward wall motion with thinning).

Images were reviewed by two experienced investigators who were unaware of the clinical and angiographic data. Agreement between the two observers was required for the classification of the wall motion abnormalities. In cases of disagreement the opinion of a third investigator was considered. An ischemic response was defined as a stress-induced new wall motion abnormality or a worsening of a wall motion abnormality at rest.

The location of the wall motion abnormalities was correlated with coronary arterial distribution by using the same methodology as described by Segar et al (13), after a modification of the scheme of Bourdillon et al (17). The apical lateral and apical inferior segments were considered to be areas of overlap. The apical lateral segment was considered to be a part of the left anterior descending coronary artery territories in association with additional septal or anterior wall motion abnormalities. The same segment was considered to be part of the left circumflex coronary artery distribution in association with posterior or posterolateral wall motion abnormalities. The apical inferior segment was related to the right coronary artery system if there were additional inferior wall motion abnormalities and to the left anterior descending region in the presence of anterior or anteroseptal wall motion abnormalities.

Quantitative Coronary Angiography. All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, The Netherlands). The automated edge detection and videodensitometric techniques of this system have been validated and described in detail elsewhere (18-22). All measurements were performed from end-diastolic frames with optimal vessel opacification.

Edge detection. A region of interest of 512X512 pixels was selected and digitised using a high-fidelity charge coupled device (CCD) videocamera. The luminal edges were detected on the basis of a weighted sum of the first and second derivative function of the brightness profile of each scanline perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using the catheter tip as a scaling device. A computer derived estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated reference diameter. This technique is based on a computer-derived estimation of the original values over the analyzed region. The calculation is based on a first degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment followed by a translation to the 80th centile level.

Videodensitometry. Densitometry is based on the approximate linear regression that exists between the optical density of a contrast enhanced lumen and its absolute dimensions. In order to follow this approach, the brightness of each scanline perpendicular to the vessel centerline was transformed into an absorption profile using a simple logarithmic transfer function to correct for the Lambert-Beer law. The background contribution was estimated by computing the linear regression line through the background pixels located left and right of the detected luminal contours. By subtracting this background portion from the absorption profile of the vessel a net cross-sectional absorption profile was calculated. A cross-sectional area function of the analyzed segment was obtained by repeating this process with all scan-lines. An interpolated reference area was calculated from the reference diameter assuming a circular cross section. The cross-sectional area at the narrowest point was identified and expressed in mm2.

Data analysis. All continuous variables were expressed as mean ± SD. The two-tailed Student's t test was used for analysis of continuous data. The chi-square test and Fisher's exact test were used to compare differences between proportions. The independent correlation of the angiographic parameters to the percentage of the maximal age-predicted heart rate was determined by logistic regression analysis. Angiographic variables were entered as categorical variables by use of their respective cut-off values. These values were achieved by determining for each variable the point of the maximal sum of sensitivity and specificity, when the sensitivity is equal to or greater than the specificity. Furthermore, receiver operator characteristics (ROC) curve analysis as an objective method for determining the value of the various angiographic parameters in the prediction of an abnormal dobutamine stress test was applied. This technique is independent of definitions of cut-off values. The sensitivity (true positives) is plotted against one minus specificity (true negatives) during the whole range of measurements of a specific parameter. Odds ratio and 95 % confidence intervals, were calculated, for the comparison of the relative predictive power of the best cut-off value of each angiographically determined variable. A p value of < 0.05 was considered statistically significant. The statistical package used was SAS, release 6.04, North Carolina, USA.

Results

Results of Dobutamine-atropine Stress Test. Dobutamine-atropine stress echocardiography was positive in 18 patients. There were no significant differences in age, gender, or the affected coronary artery between patients with a positive (group 1) or negative (group 2) test. Beta-blockers were part of the antianginal therapy in 24 (70%) patients. Of these, 10 patients (4%) developed a positive dobutamine stress test compared with 14 (58%) with a negative test (ns).

Table 1 summarises the results of the dobutamine-atropine stress test. The percentage of the maximal age-predicted heart rate achieved was noted to be significantly higher (82±14) in group 1 than in group 2 (69±17) ($p<0.05$) and in patients without beta-blocker therapy (87±9 versus 72±17; $p < 0.05$). Atropine was added in 15 patients. (12 were on beta-blocker therapy). However, since the presence and severity of the disease is the main determinant of a positive test, the achievement of the target heart rate was not found by logistic regression analysis to be an independent predictor of a positive stress test. In figure 1, the evolution of the heart rate during the test is shown. Although the maximal heart rate when atropine was added was higher, it did not change the sensitivity of the test. It was also evident, that patients taking beta-blockers frequently need atropine at the end of the test in order to achieve the target heart rate. During the test, angina occurred in 11 patients (32%) with equal distribution in the two groups (6 patients in group 1, and 5 in group 2, p = ns). An ischemic electrocardiographic response during stress testing occurred in 8 patients (24%) and again there were no significant differences between the two groups (5 patients in group 1, and 3 patients in group 2, p = ns).

	Group 1 (n = 18)	Group 2 (n = 16)
% Maximal heart rate	82 ± 14	69 ± 17*
Stress angina	6 (18%)	5 (15%)
Ischemic ST segment deviation	5 (15%)	3 (9%)
Atropine	8 (53%)	7 (47%)

*$p < 0.05$. Data presented are mean value ± SD or number (%) of patients.

Table 1 - Results of Dobutamine Strees Test in Study Groups 1 and 2.

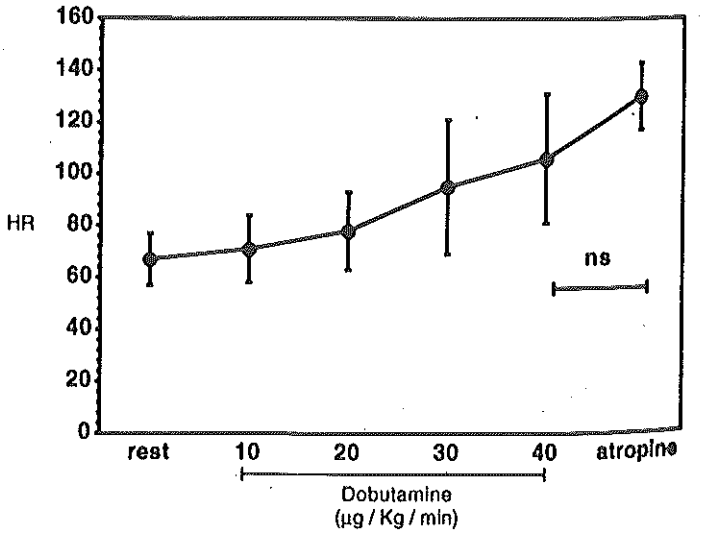

Figure 1 - Evolution of heart rate (HR) during dobutamine infusion and atropine administration. Clearly seen is the steep increase in heart rate with the addition of atropine, although the difference in maximal heart rate between patients who did and did not receive atropine was not statistically significant.

Results of Quantitative Angiography. For the entire population, quantitative coronary angiography revealed a mean percent diameter stenosis of 56±20% (range 11% to 100% - 4 patients with total occlusion), a mean percentage area stenosis of 74±20% (range 24% to 100%). a mean minimal lumen diameter of 1.01±0.59 mm (range 0 to 2.84 mm) and a mean reference diameter of 2.41±0.52 mm (range 1.64 to 4.07 mm).

Figure 2 shows the relationship between the sensitivity and specificity of the dobutamine-atropine stress test and their receiver operator characteristics curves for each of the angiographic indices, as a function of stenosis severity. For clinical purposes, a cut point is often selected to permit computation of sensitivity and specificity, parameters that are widely employed and understood in the medical literature (23). There are two commonly used schemes for selecting cut points in this setting. The first involves the choice of a convenient but arbitrary point, such as 50% diameter stenosis. The second uses the intersect of the sensitivity and specificity curves as the cut point (24). In the present study an alternative approach was used based on receiver operator characteristics curves. We selected the point at which the sum of the sensitivity and specificity, when the sensitivity is equal to or greater than the specificity reaches a maximum. As this point takes into account the shape of the two curves near the point of interception (figure 2) it was hoped that this technique will provide better diagnostic accuracy. As an example in figure 2, if we select the

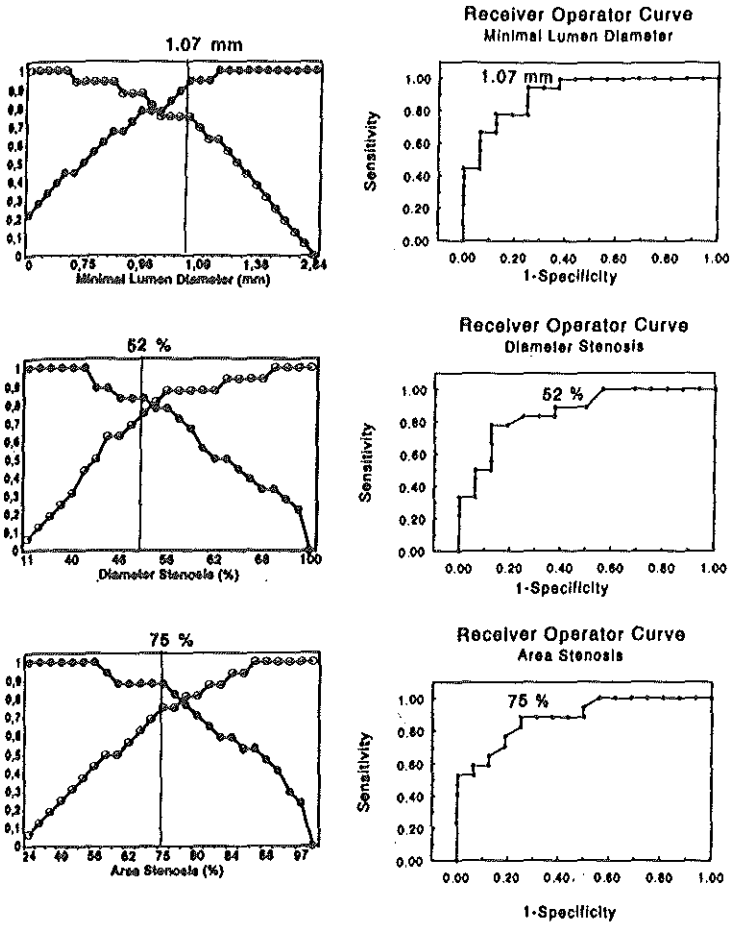

Figure 2 - Relation between the sensitivity and specificity of the dobutamine-atropine stress test and the receiver-operator curves for each of the angiographic indexes as a function of stenosis severity. **Left,** Variation in sensitivity (**solid circles**) and specificity (**open circles**) are presented as a function of cutoff points for the different quantitative agiographic variables. **Right,** Corresponding receiver-operator curves for the angiographic variables.

interception of the sensitivity and specificity curves, the sum will be 159 points (sensitivity 78 + specificity 81). Using our approach, the sum of the sensitivity and specificity will be 169 (sensitivity 94 + specificity 75).

All the quantitative angiographic parameters revealed a high sensitivity (ranging from 82-94 %) for the identification of ischemia - induced wall motion abnormalities. While all the angiographic variables had the same specificity (75 %), minimal lumen diameter had the highest sensitivity (94 %). Because patients with normal coronaries were not included in the study, the specificity value is probably underestimated.

Table 2, summarizes the relationship of different cut-off points to the outcome of the stress test. Minimal lumen diameter has a predictive value which is considerably larger (odds ratio 51), than the commonly used parameters of relative obstruction (odds ratio of 15 and 23 for percent diameter and percent area stenosis respectively).

Angiographic Cutoff Values	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio
MLD ≤1.07 mm	94 (84–100)	75 (54–96)	81	92	51 (4–1,929)
A Ste ≥75%	88 (73–100)	75 (54–96)	79	86	23 (2–242)
D Ste ≥52%	83 (66–100)	75 (54–96)	79	80	15 (2–123)

Numbers in parentheses are 95% confidence intervals. A Ste = area stenosis; D Ste = diameter stenosis; MLD = minimal lumen diameter.

Table 2 - Quantitative Angiographic Results According to Cutoff Values.

Discussion

Dobutamine Stress Echocardiography. The use of dobutamine stress echocardiography in the assessment of myocardial ischemia offers advantages over the traditional nuclear techniques, including lower cost, less time consuming, no radiation exposure and greater availability, which justify its growing application in clinical practice (6-10,12,13). Because wall motion abnormalities are an early and specific indicator of myocardial ischemia, dobutamine stress echocardiography is potentially superior to stress scintigraphy, since, particularly in patients with mild to moderate stenoses, transient perfusion defects result from a maldistribution of coronary flow, and do not necessarily reflect "true" myocardial ischemia. In addition, SPECT myocardial scintigraphy is associated with a lower specificity when compared with dobutamine stress echocardiography in patients with single coronary stenosis (25-26).

In the study population the incidence of chest pain and ischemic electrocardiographic response during dobutamine echocardiography was low (32% and 24% respectively) and without relation to the outcome of the echo stress test. This is not surprising, since also in previous works the sensitivity and specificity of stress induced ECG changes in single vessel disease were relatively low (27-30). The finding of a significant higher heart rate in patients who developed wall motion abnormalities during dobutamine stress echo underlines the importance of chronotropism as an additional mechanism to increase inotropism to induce ischemia. This is in agreement with previous experimental and clinical data (16,31,32).

Previous Studies. In previous studies, quantitative angiographic measurements of stenosis severity correlated well with the outcome of stress echocardiography (13, 15). In a population of 25 patients with single vessel disease, Ryan et al (14), using the criteria of more than 50% visually determined percent diameter stenosis, found a sensitivity of 76% of exercise echocardiography. Sheikh et al (15), studying 34 patients with single vessel obstruction, reported that all patients with more than 75 % diameter stenosis by visual assessment developed wall motion abnormalities during exercise echocardiography. However, only 50 % of the same patients had an abnormal test if the angiographic cut-off criterion was lowered to 50 % diameter stenosis. In a subgroup of 30 patients with normal left ventricular function at rest and single or multivessel disease, Segar et al (13) described a high sensitivity (90 %) of dobutamine stress test to detect significant coronary disease using a diameter stenosis of more than 50% by quantitative angiography. Several authors (8,10,12,16) using the same approach reported a wide variation of the sensitivity values for the detection of significant lumen reduction. All these studies, however, relied on arbitrary cut-off points for the determination of a significant stenosis, and few evaluated (13,15) absolute parameters of luminal obstruction. The high sensitivity and specificity noted for minimal lumen diameter in our study (94% and 75 % respectively), although using a different approach, are in accordance with Segar et al (13) who reported a high sensitivity of the dobutamine stress test in the identification of coronary stenoses using a cut-off criterion of 1.0 mm for minimal lumen diameter, although in this study an attempt to determine the best cut-off point was not reported.

Relative versus Absolute Measurements of Coronary Stenosis. It is known that in the setting of diffuse coronary disease relative parameters of luminal narrowing may underestimate the functional impact of stenosis severity (33-35). In this study, only patients with single discrete stenosis were included, therefore it is of greater significance that minimal lumen diameter was found to be the best predictor of an abnormal stress test. However, even in the presence of focal disease, angiographically normal segments used in the determination of the relative measures of luminal obstruction are frequently involved in the atherosclerotic process as reported in several intracoronary echocardiographic studies (36,37). Therefore, absolute dimensions may be a better indicator of the physiological importance of coronary stenoses in medium to large arteries. Our finding that a minimal lumen diameter of less than or equal to 1.07 mm is the best parameter for the prediction of ischemia-induced wall motion abnormalities, supports this hypothesis. In this regard, data derived

from the MERCATOR study (38) revealed that patients with a minimal lumen diameter less than 1.1 mm at the follow-up had a higher occurrence of subsequent clinical events. Although it has been reported that the sensitivity of a visually determined diameter stenosis of more than 50 and less than 70 % is low for the occurrence of new wall motion abnormalities during stress echocardiography (15), the finding in our study of a cut-off point of 52 % for the diameter stenosis is in agreement with previous experimental work showing a decline in coronary flow reserve at this level (39), and confirms that for this range of obstructions, visual assessment overestimates quantitative measurements (4,5).

Edge Detection versus Videodensitometry in Angiographic Analysis. Serruys et al (40) and Wijns et al (41), reported that a videodensitometrically determined area of obstruction > 80 % constituted a physiologically significant obstruction as assessed by exercise - redistribution thallium scintigraphy, and these data concord with our criteria of 75 % reduction in cross sectional area for the prediction of ischemia-induced wall motion abnormalities. Videodensitometrical determination of percent area obstruction is theoretically independent of the geometrical shape of the luminal obstruction, having the potential to overcome limitations related to edge detection techniques, when using a single projection. Because in our study an average of two projections was used to determine the different angiographic parameters, and because situations where the occurrence of a complex luminal shape were not included in the analysis (eg: post-angioplasty, unstable angina), there was no clear advantage of the densitometric determined percent area stenosis over the percent diameter stenosis.

Conclusions. Quantitative angiography provides an objective assessment of the functional significance of coronary stenoses as determined by dobutamine stress echocardiography. Although relative measurements of lumen obstruction are predictive of an abnormal stress echocardiogram, minimal lumen diameter appears to be the optimal parameter in the determination of the physiological significance of coronary stenoses in medium to large arteries.

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CHAPTER VII

IMPROVED IDENTIFICATION OF CORONARY ARTERY DISEASE IN PATIENTS WITH COMPLETE LEFT BUNDLE BRANCH BLOCK BY USE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY; A COMPARISON WITH MYOCARDIAL PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY*

Abstract

Objectives: This study was conducted to compare the efficacy of dobutamine stress echocardiography with that of perfusion tomography for the non-invasive identification of coronary artery disease in patients with left bundle branch block.

Background: False positive perfusion defects are common in the territory of the left anterior descending coronary artery in patients with left bundle branch block. Preliminary data have suggested that dobutamine stress echocardiography may provide an accurate means of identifying coronary disease in these patients. However, these techniques have not been compared in the same patients with left bundle branch block.

Methods: Twenty-four patients with complete left bundle branch block were studied prospectively with dobutamine stress echocardiography and single-photon emission computed tomography. Eleven patients had a previous myocardial infarction. The presence of coronary artery disease (> 50 % coronary stenoses at coronary angiography) was compared with the presence of fixed or reversible perfusion defects, and with resting or dobutamine-induced abnormalities of wall thickening. For each test, the left anterior coronary artery territory was compared with the circumflex and/or right coronary artery.

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Results: Significant coronary artery disease was found in the circumflex and/or right coronary artery in 13 patients, 11 (85 %) were identified both by perfusion imaging and dobutamine echocardiography. In the 11 patients without circumflex and/or right coronary artery disease, scintigraphy was positive in 4 (specificity: 64 %), and dobutamine echocardiography in 3 (specificity: 73 %, p = NS). Significant coronary artery disease was found in the left anterior descending coronary artery in 12 patients, all (100 %) were identified by perfusion imaging and 10 (83 %, p = NS) by dobutamine echocardiography. In the 12 patients without left anterior descending coronary artery disease, scintigraphy was also positive in all (specificity: 0 %), and dobutamine echocardiography in only 1 (specificity: 92 %, $p < 0.01$). Their diagnostic accuracy was 50 % and 87 % ($p < 0.05$) respectively. This low specificity of perfusion tomography was partially corrected by restricting the diagnosis of coronary disease to those patients with partially reversible defects or with an associated apical defect to indicate left anterior descending coronary artery disease.

Conclusions: Dobutamine stress echocardiography, using wall thickening impairment to define coronary artery disease, is more specific and accurate than conventional perfusion tomography for the non-invasive identification of coronary artery disease in the left anterior descending artery of patients with left bundle branch block.

Introduction

Left bundle branch block is known to be a strong predictor of cardiovascular mortality, especially when associated with coronary artery disease (1-3). However, the ability of non-invasive tests to diagnose coronary artery disease in these patients has been disappointing. Exercise-induced changes in the electrocardiogram are non diagnostic in the presence of left bundle branch block (4). Exercise perfusion scintigraphy has been proposed as an alternative method, but several studies have reported false positive anteroseptal and septal perfusion defects, despite an angiographically normal left anterior descending coronary artery (5-11). This phenomenon is thought to be related to asynchronous septal contraction due to the left bundle branch block.

Dobutamine stress echocardiography has been widely accepted as a safe, sensitive and specific technique for detecting coronary artery disease and for identifying disease in individual coronary arteries (12-14). Two-dimensional echocardiography is able to recognize the typical asynchronous septal contraction due to the left bundle branch block (15,16), despite which myocardial thickening is preserved in

the absence of coronary artery disease (17). Preliminary data (18) have indicated that stress echocardiography, using wall thickening impairment to identify coronary artery disease could be the investigation of choice for the non-invasive identification of coronary artery disease in patients with complete left bundle branch block. The present study thus compared the accuracy of dobutamine stress two-dimensional echocardiography with that of single photon emission computed tomography for the detection of left anterior descending coronary artery disease in patients with left bundle branch block, and further evaluated the diagnostic accuracy of dobutamine stress echocardiography in the other vascular territories.

Methods

Patient Population. Twenty-four patients with permanent complete left bundle branch block were studied with dobutamine stress two-dimensional echocardiography, perfusion tomography and coronary arteriography in our two institutions between July 1991 and January 1994. There were 18 men and 6 women of mean age 61 ± 9 years (range from 31 to 75 years). Angiograms were reviewed by experienced observers who were unaware of the dobutamine results. Coronary stenosis were quantitated visually and coronary artery disease was defined by > 50 % luminal diameter stenosis of a major epicardial coronary segment.

Patients were separated into 2 groups, according to the presence or absence of previous history of myocardial infarction.

- *Group I* comprised 13 patients without myocardial infarction studied for the diagnosis of coronary artery disease. Their pre-test disease probability, calculated for each patient based on age, gender, and symptoms (19), was 50 ± 33 %. Significant coronary artery disease was present in 5 patients, 2 patients had single left anterior descending artery disease, 2 patients had two vessel disease, and one patient had three vessel disease.

- *Group II* comprised 11 patients with a previous history of myocardial infarction. All but one of them had significant coronary stenoses. Five had two vessel disease, and the remaining 5 had three vessel disease.

Dobutamine stress. The dobutamine stress test was performed using a standard protocol. Before starting the test, the clinical history was recorded, a resting electrocardiogram and echocardiogram were performed, and intravenous access was secured. Dobutamine was infused in 3 minute dose increments of 5, 10, 20, 30, and 40 µg/kg/min. In 7 patients, an additional increase of rate-pressure product was

obtained by repetitive injections of 0.25 mg of atropine, up to a maximum dose of 1 mg (20). Blood pressure and a three channel ECG were monitored throughout the test. Endpoints were achievement of maximal dose, severe angina, or the development of intolerable side-effects, including a significant drop of systolic blood pressure, or life-threatening arrhythmias. The isotope was injected intravenously one to two minutes before completion of the stress. If severe angina necessitated early termination of the test, dobutamine was continued at a lower dose for one minute after the isotope was injected.

Perfusion Scintigraphy. A dose of 20 mCi of technetium 99m methoxy isobutyl isonitrile (MIBI) was injected in 21 patients. Stress perfusion scintigraphy was performed 1 to 2 hours later, and rest imaging was performed on another day. In 3 patients [17,19,20], 2 mCi of Thallium-201 was used instead of MIBI. In these patients, stress perfusion imaging was begun within 10 minutes after the end of the stress, and rest imaging was performed 4 hours later, 30 minutes after the reinjection of 1 mCi of thallium-201. Single photon emission computed tomography was acquired over 180 degrees, using large field, single crystal cameras (General Electric 400 AC/T, or Siemens Orbiter) and either high resolution collimator (n = 11), or low-energy all purpose collimator (n = 13). Transaxial images were obtained by back-projection and reconstructed into short-axis, and vertical and horizontal long axis views.

Perfusion scintigrams were interpreted by the consensus of 3 experienced observers unaware of the clinical, echocardiographic, and angiographic data. Vascular territories were ascribed to scintigraphic imaging by the conventional method (21). Each short axis view was divided into 6 segments. The left anterior descending coronary artery territory was represented by the anterior segments and the upper and lower septum. The right coronary artery was assigned the inferior segments and the basal part of the lower septum, and the left circumflex artery, the posterior and lateral segments. The vertical and horizontal long axis views were only used to characterize the apex, which was assigned to the left anterior descending coronary artery. Three different approaches were used to identify coronary artery disease.

- *Method A (conventional approach):* Coronary artery disease was identified by any perfusion defect.

- *Method B ("reversible" approach):* Perfusion defects had to be at least partially reversible at rest to evoke a diagnosis of coronary artery disease. Fixed perfusion defects were considered as non-diagnostic.

- *Method C ("apical" approach):* According to the new method suggested by Matzer (8), left anterior descending coronary artery dis-

ease was considered present only when the apex of the left ventricle was abnormal, irrespective of the reversible or irreversible nature of the defect.

Stress echocardiography. Two-dimensional echocardiographic images were acquired in parasternal long and short axis, and apical 4 and 2 chamber views. These were recorded on tape and digitized online at baseline, low and high dobutamine doses, and after the addition of atropine. Images were interpreted for the presence of coronary artery disease by the consensus of 3 experienced observers, blinded to all clinical, scintigraphic, and angiographic data. A normal response was defined by an enhancement of wall thickening with stress. Heterogeneity of septal contraction was not regarded as a possible marker of coronary artery disease. An ischemic response was identified by stress-induced wall thickening impairment, including failure to improve wall thickening relative to hyperkinetic response to maximal stress. Infarction was characterized by failure of wall thickening associated with akinesis or dyskinesis at rest.

Regional function was interpreted in 16 myocardial segments: septal, lateral, inferior, and anterior at the apex, and these segments as well as anteroseptal and posterior segments at the base and mid-papillary muscle level. These were combined to reflect vascular territories using the same segmentation as that employed for perfusion scintigraphy. Thus, the same assumptions were made about the coronary artery distribution.

Statistical analysis. The sensitivity, specificity, accuracy, positive and negative predictive values of dobutamine stress perfusion tomography and echocardiography were obtained in the usual fashion. For each test, the left anterior descending coronary artery was compared with the left circumflex and/or right coronary arteries. The results of each test are compared using the Mc Nemar test for paired data. To avoid limitations due to the normal approximations rule for proportions (22), we used the Youden index to compare individual patients. The Youden Index, which is not influenced by prevalence, was calculated using the formula:

Youden Index = Sensitivity + Specificity - 100.

Continuous variables are expressed as mean ± one standard deviation, and compared with a paired t-test.

Results

Dobutamine stress response. During the dobutamine test, heart rate increased from 74 ± 14 to 129 ± 22 bpm ($p < 0.001$), systolic blood pressure increased from 133 ± 25 to 145 ± 31 mmHg ($p < 0.01$), and the rate-pressure product from 10,157 ± 3,447 to 18,784 ±

4,966 bpm.mmHg ($p < 0.001$). Chest pain occurred in 9 patients (6 of whom had coronary artery disease), and was of sufficient severity to provoke premature termination of the test in 4. Prediction of coronary artery disease based on dobutamine-induced chest pain alone gave a sensitivity of 37 %, a specificity of 67 %, an overall accuracy of 46 %, and a Youden Index of 4.

Detection of coronary artery disease in the left anterior descending coronary artery territory. Left anterior descending coronary artery disease was identified in 12 patients. Septal perfusion defects were present in all 24 patients. Thus, using the conventional method A, sensitivity was 100 %, specificity was 0 %, and accuracy was 50 %. In 9 patients with and in 1 patient without left anterior descending artery disease, this defect was found to be at least partially reversible. Using the "reversible" approach B, sensitivity was 75 %, specificity was 92 % ($p < 0.001$ vs A), and accuracy was 83 % ($p < 0.001$ vs A). There was an associated apical defect in 11 patients with and in 6 patients without left anterior descending artery disease. The "apical" approach C gave a sensitivity of 92 %, a specificity of 50 %, and an overall accuracy of 71 %.

At stress echocardiography, 10 patients with left anterior descending coronary artery had dobutamine-induced wall thickening impairment, while a false positive response was noted in 1 patient. Thus, sensitivity was 83 %, specificity was 92 % ($p < 0.01$ vs A), and accuracy was 87 % ($p < 0.05$ vs A). The positive predictive value was 91 %, and the negative predictive value was 85 %. A comparison between these 4 methods is provided in figure 1, and individual data are provided in table 1.

Detection of coronary artery disease in the left circumflex and/or right coronary artery territory. Significant coronary stenoses were found in the left circumflex and/or right coronary artery territory in 13 patients. Any type of perfusion defects were present in 11 of these, but also in 4 of the 11 patients without left circumflex and/or right coronary disease. Using the conventional approach A, sensitivity was 85 %, specificity was 64 %, and accuracy was 75 %. Only 1 of these true positive, and 2 of the false positive defects were partially reversible on the resting scan. For the "reversible" approach B, sensitivity was 8 % ($p < 0.01$ vs A), specificity was 82 %, and accuracy was 42 % ($p < 0.05$ vs A).

At dobutamine echocardiography, 11 patients with left circumflex and/or right coronary artery disease had corresponding wall thickening impairment, while false positive responses were noted in 3 patients. Sensitivity was 85 % ($p < 0.01$ vs B), specificity was 73 %, and accuracy was 79 % ($p < 0.05$ vs B). The positive predictive value was 79 %, and the negative predictive value was 80 %. A comparison

Pt	MI	LAD					LCX/RCA			
		An	SPECT A	SPECT B	SPECT C	2DE	An	SPECT A	SPECT B	2DE
1	0	0	+	0	0	0	0	0	0	0
2	0	0	+	0	0	0	0	0	0	0
3	0	0	+	0	0	0	0	0	0	+
4	0	0	+	0	0	0	0	0	0	0
5	0	0	+	0	0	0	0	0	0	0
6	0	0	+	0	+	0	0	0	0	0
7	0	0	+	0	+	0	0	+	0	0
8	0	0	+	0	0	0	0	0	0	0
9	0	+	+	+	+	0	0	+	+	0
10	0	+	+	0	+	+	0	+	0	+
11	0	+	+	+	+	+	+	0	0	0
12	0	0	+	0	+	0	+	+	0	+
13	0	+	+	+	+	+	+	0	0	+
14	+	0	+	0	+	+	+	+	0	+
15	+	0	+	+	+	+	0	+	+	+
16	+	+	+	+	0	0	+	+	0	+
17	+	+	+	+	+	+	+	+	+	+
18	+	0	+	0	+	0	+	+	0	+
19	+	+	+	+	+	+	+	+	0	+
20	+	+	+	+	+	+	+	+	0	+
21	+	+	+	0	+	+	+	+	0	+
22	+	+	+	0	+	+	+	+	0	0
23	+	+	+	+	+	+	+	+	0	+
24	+	+	+	+	+	+	+	+	0	+

Table 1 - Individual patient data.

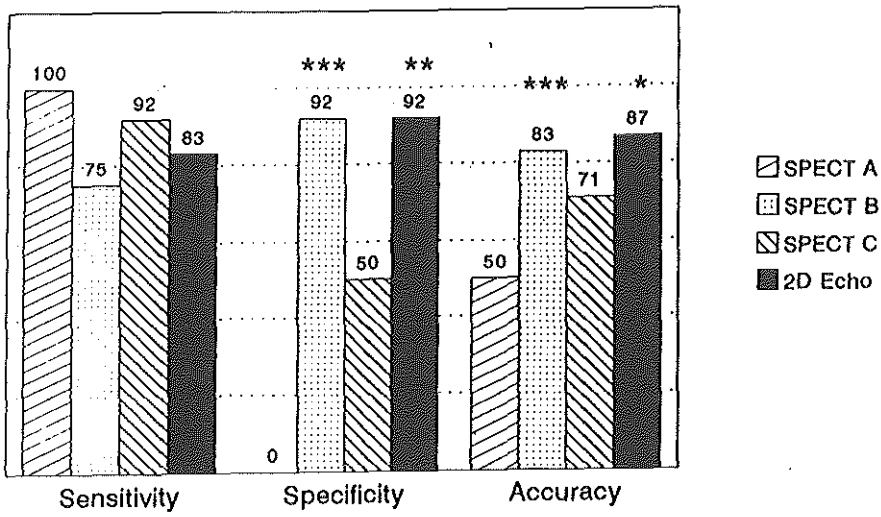

Figure 1 - Comparision between Tc99m-MIBI tomography, and stress echocardiography for the localisation of coronary artery disease in the left anterior descending coronary artery.
SPECT A, B, and C represent the three scintigraphic criteria (see text); 2D Echo, stress echocardiography.
***, $p < 0.001$; **, < 0.01; *, < 0.05 versus A.

between the accuracy of stress echocardiography and the two scintigraphic approaches in the right and circumflex artery distributions is shown in figure 2.

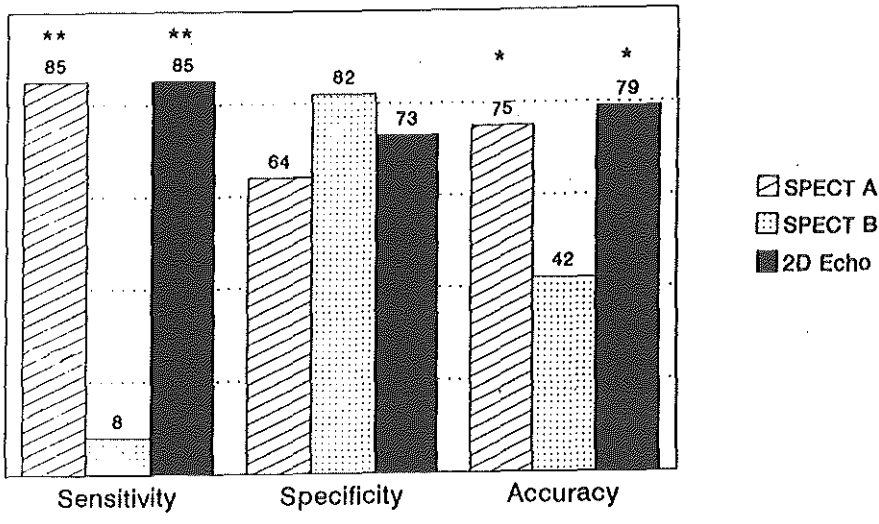

Figure 2 - Comparison between Tc99m-MIBI tomography, and stress echocardiography for the localisation of coronary artery disease in the left circumflex and/or right coronary artery.
SPECT A, and B represent the two scintigraphic criteria (see text); 2D Echo, stress echocardiography.
**, $p < 0.01$; *, < 0.05 versus B.

Identification of coronary artery disease in individual patients.

Group I: In the 8 patients without coronary artery disease, specificity was 0 % for the scintigraphic approach A, 75 % for the approach B, 100 % for the approach C, and 87 % for dobutamine echocardiography. In the 5 patients with coronary artery disease, but without myocardial infarction, sensitivity was 100 % for the conventional scintigraphic approach A, 100 % for the "reversible" approach B, 60 % for the "apical" approach C, and 80 % for dobutamine echocardiography. Accuracy was 38 %, 84 %, 84 %, and 84 % respectively. The Youden indices were 0, 75, 60, and 71.

Group II: One patient [15] with a history of previous myocardial infarction had no significant coronary artery stenosis and evoked false positive responses using all techniques. In the remaining 10 patients with significant coronary artery disease, all had some kind of perfusion defect, and it was partially reversible in at least one of the vascular territories in 6 of them. Sensitivity was 100 %, 60 % and 100 % for the scintigraphic approaches A, B, and C. All of these patients also showed stress-induced wall thickening impairment, giving a sensitivity of 100 % for dobutamine echocardiography.

Group I + II: When data of patients with and without history of previous myocardial infarction are combined, the accuracy of the scintigraphic approaches A, B, and C, and that of dobutamine echocardiography were respectively 67 %, 92 %, 75 %, and 92 %. The Youden indices were 0, 75, 62, and 81 respectively.

Discussion

These data confirm the lack of accuracy of conventional myocardial perfusion tomography for the non-invasive identification of coronary artery disease in patients with left bundle branch block. This is mainly explained by the poor specificity of perfusion defects in the left anterior descending coronary artery territory. The specificity of scintigraphy was enhanced by restricting the diagnosis of coronary disease to those patients with partially reversible defects, or an associated apical defect to indicate left anterior descending coronary artery disease. Dobutamine echocardiography, using the presence of impaired wall thickening to define coronary artery disease, has significantly superior accuracy for the localization of coronary artery disease in different vascular territories. In individual patients however, stress echocardiography and the two alternative scintigraphic approaches had comparable accuracy.

Conventional scintigraphic results. False positive perfusion defects have been reported repeatedly in patients with left bundle branch block and no coronary artery disease (5-11). The present study,

reporting a 100 % incidence of septal defects on the post-stress scan, irrespective of the coronary anatomy thus confirm these previous observations. Various mechanisms have been proposed to explain these false positive myocardial perfusion defects. First, a reduction of myocardial blood flow within the intraventricular septum was observed during rapid pacing and artificial induction of left bundle branch blocks in dogs (6). While the underlying pathophysiology is controversial (23), this reduction of perfusion is thought to reflect an increased systolic and reduced diastolic time in the septum due to the conduction defect. Other causes of false positive perfusion defects include partial volume effects, camera field nonuniformity, patient motion during imaging, or an incorrect definition of the long axis of the left ventricle. Finally, we can not exclude a possible role of microvascular insufficiency, myocardial cell dysfunction (24) or septal fibrosis (25) which have been sometimes observed in patients with complete left bundle branch block.

In the present study, perfusion scintigraphy was performed using computed tomography. This approach is now well established as being superior to planar imaging for the detection and sizing of perfusion defects (26), and this superiority is mainly due to the higher image contrast resolution and improved definition of individual vascular territories afforded by tomography. The 0 % specificity found in the left anterior descending coronary artery territory contrasts with a few studies using planar imaging and reporting a lesser incidence of septal defects (11, 27). However, recent studies using computed tomography have reported comparable results. DePuey, using exercise thallium-201 in 10 patients without left anterior descending coronary artery disease reported a 90 % false positive rate in the corresponding vascular territory (7). This high incidence of false positive perfusion defects with exercise thallium-201 perfusion tomography was confirmed by Burns (9) in 70 % of patients by visual analysis, and in 80 % by quantitative analysis; and by Matzer, who demonstrated, using the conventional visual approach, a 86 % false positive rate for left anterior descending coronary disease (8).

Alternative scintigraphic criteria. In the present study, we also evaluated the diagnostic accuracy of reversible perfusion defects for the diagnosis and localisation of coronary artery disease *(Method B).* In the left anterior descending coronary artery territory, all but one false positive septal perfusion defects were found to be fixed, while 3 true positive defects were partially reversible. Accuracy thus significantly increased in comparison with the conventional analysis. However, in the left circumflex and/or right coronary artery territory, despite the low incidence of false positive defects, only one true positive perfusion defect was found to be partially reversible.

Obviously is this related to the high proportion of patients with previous myocardial infarction included into this study. However, why this high proportion of true positive fixed defects was not observed in the left anterior descending coronary artery remains elusive.

To avoid isolated septal defects as possible source of false positive tests, Matzer required the apex to be abnormal to indicate left anterior descending coronary artery disease *(Method C)*. In that study, specificity improved from 14 % to 79 % ($p < 0.001$) by visual analysis and from 14 % to 64 % ($p < 0.01$) by quantitative analysis (8). We tested this method in the present study and confirmed an improved specificity from 0 % to 50 % in the 12 patients without left anterior descending coronary artery disease. Accuracy also increased from 50% to 71% compared with the conventional approach. However, this improvement failed to reach statistical significance.

The present results thus suggest that, in the presence of a known left bundle branch block, alternative scintigraphic interpretations should be used in the left anterior descending coronary artery territory; but that the conventional approach should still be preferred in other vascular territories.

Echocardiographic assessment. Septal wall motion abnormalities, with delayed contraction of the left side of the septum and the left ventricular free wall are well known in patients with left bundle branch block (15,16). However, myocardial thickening is supposed to remain normal or nearly normal in the absence of coronary artery disease (17). Exercise-induced wall motion abnormalities were previously evaluated using gated radionuclide ventriculography in patients with permanent or rate-dependent left bundle branch block (28,29). These studies have confirmed that the ability to increase ejection fraction was impaired in these patients, even in the absence of coronary artery disease.

The present study specifically evaluated the diagnostic value of stress-induced wall thickening abnormalities using dobutamine echocardiography in patients with left bundle branch block. Using this criterion, both left anterior descending and left circumflex and/or right coronary artery disease were identified with adequate sensitivity and specificity. On a patient-based analysis, the diagnostic accuracy of dobutamine echocardiography was superior to that of the conventional scintigraphic approach: 84 % vs 38 % in patients without previous myocardial infarction, and 92 % vs 67 % when patients with previous myocardial infarction were included. However, it was comparable with that of the two alternative scintigraphic approaches (B and C). This last finding thus indicate that, despite inadequate localisation of coronary stenoses, patients with and without coronary artery disease were similarly recognised as such, either by dobutamine echocardiography, or by the two alternative scintigraphic approaches.

Use of dobutamine stress. Dobutamine stress echocardiography has been extensively validated as a sensitive and specific method for the non-invasive diagnosis and identification of coronary artery disease (12-14). In patients able to exercise, however, the exercise stress echocardiography is known to be of superior diagnostic accuracy (30). In the present study, we preferred dobutamine to exercise for two reasons: first, DePuey reported more marked septal perfusion abnormalities in patients achieving very high peak heart rates (>170 bpm) during exercise (7), which are infrequent with dobutamine (31). Second, superior echocardiographic images are required to allow wall thickening instead of wall motion assessment, and image quality is easier to obtain during pharmacological testing than during exercise assessment. This possible benefit of pharmacological stress was indeed already suggested by Pellika (32) for dobutamine echocardiography, and by Burns (10) for dipyridamole thallium-201 perfusion tomography.

Study limitations. Inclusion of patients with previous myocardial infarction into the present study could appear as a possible study limitation. However, both imaging modalities were tested in the same patients, and the main issue of this study was not only to establish the diagnostic accuracy of dobutamine echocardiography, but more to compare it with that of perfusion tomography. The same limitations thus similarly affected both imaging techniques. Moreover, dobutamine echocardiography was similarly more accurate than conventional perfusion tomography for the non-invasive diagnosis of coronary artery disease in the 13 patients with a pretest probability of disease of 50 ± 33 % (Group I) and in the entire population (Group I + II). A second possible study limitation is the use of two different isotopes for the scintigraphic assessment. Thallium-201 is indeed supposed to produce more fixed defects at 4 hour imaging due to late redistribution. However, only 3 of the 24 patients were studied with thallium-201 and in all three cases, left anterior descending coronary artery perfusion defects were found to be at least partially reversible.

Conclusions

The present study is the first one, to our knowledge, to specifically evaluate the diagnostic accuracy of dobutamine stress echocardiography in patients with left bundle branch block, and to compare it with three different scintigraphic approaches. In these patients, conventional scintigraphic interpretation produces a prohibitive proportion of fase positive perfusion defects in the left anterior descending coronary artery territory, and should be replaced by alternative approaches requiring partially reversible defects or an

associated apical defect to indicate left anterior descending coronary artery disease. With dobutamine stress two-dimensional echocardiography, specificity and accuracy were significantly superior to conventional myocardial perfusion tomography regarding the left anterior descending coronary artery disease, and equivalent regarding other vascular territories. Thus, dobutamine stress two-dimensional echocardiography, using wall thickening abnormalities to define ischemia, appears to be an ideal non-invasive test for the identification of coronary artery disease in patients with complete left bundle branch block.

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CHAPTER VIII

AKINESIS BECOMING DYSKINESES DURING HIGH DOSE DOBUTAMINE STRESS ECHOCARDIOGRAPHY: A MARKER OF MYOCARDIAL ISCHEMIA OR A MECHANICAL PHENOMENON?*

There is increasing evidence that dobutamine stress echocardiography is a potentially useful clinical tool for assessing the functional severity of coronary disease and myocardial viability (1-8). Therefore the idea has arisen that dobutamine stress echocardiography provides the unique opportunity to assess, with a single, easily repeatible, non-expensive and widely available method both residual ischemia and viability (5). Since that time several studies, incuding some from our group (9-12), confirmed a fair agreement between stress echocardiography with different stress modalities and perfusion scintigraphy for the diagnosis of myocardial ischemia. The specific aim of the present study was to distinguish whether the pathophysiological mechanism of an equivocal stress echocardiocardiographic finding, that of an akinetic segment at rest becoming dyskinetic during peak dobutamine test was due to ischemia or was a nonischemic mechanical event. This is a particularly important clinical topic because a correct identification of viable and jeopardized myocardium is crucial for the proper selection of coronary revascularization in patients with left ventricular dysfunction. To explore this, 20 patients with this pattern were studied with a simultaneous 2-stage (low and high dose) dobutamine stress echo and perfusion single-photon emission computed tomography (SPECT) imaging.

The study group consisted of 20 patients (15 men and 5 women; mean age 58, range 24-80), out of 560 consecutive patients referred for dobutamine stress echocardiography for the diagnosis or functional assessment of coronary disease. All these patients had a previous old myocardial infarction and a regional akinesis on resting echo becoming clearly dyskinetic during a high dose dobutamine-atropine test. At

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* Arnese M, Fioretti P., Cornel JH, Postma-Tjoa, Reijs AEM, Roelandt JRTC. Am J Cardiol 1994; 73:896-899

the time of the study the patients were off beta-blockers. All patients were studied by simultaneous echocardiography and technetium-99m isonitrile (n=16) or thallium-201 SPECT (n=4) during dobutamine-atropine infusion.

The test was performed as previously described (3,8,12). Briefly, a 2 dimensional echocardiogram was recorded at baseline, using a commercially available wide-angle phased array system (Esaote biomedica SIM 7000 CFM or Vingmed CFM 800). The following views were obtained for subsequent analysis: apical four-three-two and five chamber views. The left ventricle was divided into 14 segments and each segment was scored using a 4 point scale: 1= normal wall motion and thickening; 2= hypokinesia; 3= akinesis (absence of systolic wall motion and thickening); 4= dyskinesis (systolic outward wall motion with thinning).

Following a previously described protocol (3), dobutamine was infused through an antecubital vein cannula starting at the dose of 10 μg/kg/minute, increasing by 10 μg/kg every 3 minutes up to a maximum of 40 μg/kg/minute, which was continued for 6 minutes. In patients without side effects, myocardial ischemia or 85% of age predicted maximal heart rate, atropine (up 1 mg i.v.) was added. A 2-dimensional echocardiogram was continuously monitored and recorded on videotape for the last minute of each stage and continuously after atropine administration. The images were digitized and displayed side by side on a quad-screen, for comparison of rest and stress images. To analyze wall motion, the images recorded on videotape were subsequently reviewed at various playback speeds as well. Echocardiographic images were analyzed by 2 independent observers, blinded to the clinical data of the individual patient. Dobutamine stress echocardiography was considered "positive" when a new wall motion abnormality or a worsening of abnormal wall motion (inward motion and/or thickening) appeared in one or more segments at peak stress.

99m-technetium isonitrile (370 MBq) or 201-thallium (80 MBq) were injected intravenously 1 minute before the termination of the stress test. Post-stress SPECT imaging were acquired one hour after technetium and within 10 minutes after thallium injection respectively. A resting technetium-99m isonitrile SPECT was repeated on a separate day, while a 4 hour redistribution thallium imaging was repeated after a reinjection of 40 MBq. For each patient, six short axis slices and 3 vertical long axis slices were displayed and analyzed. As previously described (10,12), the left ventricle was divided in 47 segments and each segment was scored with a 4 point scale (from 1=normal up to 4= "absence" of uptake). The visual analysis was performed by two observers with the assistance of the circumpherential

profile analysis of the short axis slices. The apical portion was assessed only visually.

Three different responses were defined: normal, "ischemia" (transient perfusion defects), and "infarction" (fixed perfusion defect). The severity of ischemia and infarction was graded as mild, moderate and severe.

The demographic and clinical data and also the results of simultaneous dobutamine stress echo and perfusion SPECT imaging in the 20 patients are summarized in table 1.

In all patients there was an agreement between the site of the akinetic region on resting echocardiogram and of perfusion defects on the resting or redistribution SPECT images. Also the electrocardiographic site of the infarction was in all cases consistent with the imaging results.

The dobutamine stress test was uncomplicated in all cases. The highest dose was 40 μg/kg/min in 18 patients (with atropine added in 10 cases). The target heart rate was achieved in 10 patients. In 6 patients the target heart rate was not achieved despite the full dose of dobutamine and atropine, and in 4 the test was stopped because of 1) hypotension (1) or 2) electrocardiographic changes (3). Chest pain occurred in 3 patients, ST segment depression in 4 and ST segment elevation in 5.

By definition, all patients developed a worsening of the akinetic region (which became dyskinetic) while new wall motion abnormalities remote to the akinesia became apparent in 8 cases. The wall motion of the akinetic segment which became dyskinetic at peak stress did not improve at low dose dobutamine. In contrast, the wall motion of the control left ventricular regions improved in all cases, as a confirmation of the adequacy of low dose dobutamine for improving the contractility of normal myocardium. Myocardial scintigraphy showed a severe "fixed" perfusion defect in all the akinetic regions becoming dyskinetic at peak stress, consistent with a lack of scintigraphic markers of ischemia in those regions.

Dobutamine stress echocardiography is a rapidly emerging noninvasive technique for assessing patients with coronary artery disease. However, more study is required for the pathophysiological interpretation of some specific stress echocardiographic patterns. In this regard, myocardial perfusion scintigraphy, performed simultaneously with stress echocardiography provides a unique opportunity for the validation of stress echocardiographic findings (9-12).

The classical marker of myocardial ischemia by stress echocardiography is the appearance of new wall motion abnormalities

Patient	Age (yr) & Sex	ECG	Dobutamine	Atropine	Max HR	Max BP	Dyskinesis	SPECT	ChP	ST	Side Effects
1	24F	Sept	40	+	160	105/50	Apic	Apic	0	↑	0
2	42F	Ant	40	0	145	155/105	Sept-apic	Apic	0	↑	0
3	44M	Inf	40	+	148	150/80	Inf	Post	0	=	PVCs
4	44M	Ant	40	0	150	140/70	Apic	Apic	0	↓	PVCs
5	47M	Ant	30	0	134	120/60	Apic	Apic	+	↑	0
6	51M	Ant	40	+	120	120/75	Apic	Apic	0	=	0
7	54M	Inf	40	+	118	120/80	Inf	Post	0	=	0
8	57M	Ant	40	+	141	120/60	Apic	Apic	0	=	0
9	58M	Ant	40	+	95	90/50	Apic	Apic	0	=	VTs
10	61M	Inf	40	0	90	80/60	Inf	Post	0	=	Hypo
11	63F	Inf	40	+	108	140/75	Inf	Post	0	=	0
12	64M	Inf	40	+	140	145/75	Inf	Post	0	=	0
13	65M	Sept	40	0	150	110/70	Sept-apic	Apic	+	↓	0
14	65M	Ant	30	0	150	150/70	Sept	Sept	+	↓	0
15	66M	Ant	40	0	138	150/80	Apic	Apic	0	↓	AF
16	66M	Ant	40	0	133	130/70	Apic	Apic	0	=	0
17	67F	Ant	40	0	120	140/70	Ant	Ant	0	↑	0
18	68F	Inf	40	+	110	170/90	Inf	Post	0	=	VTns
19	73M	Sept	40	0	133	175/85	Apic	Apic	0	↑	0
20	80M	Inf	40	+	135	120/60	Inf	Post	0	=	AF

AF = atrial fibrillation; Ant = anterior; Apic = apical; ChP = chest pain during test; Dobutamine = maximal dobutamine dose (μg/kg/min); Dyskinesia = site of dyskinesia on echocardiography; ECG = electrocardiographic site of infarction; Hypo = hypotension; Inf = inferior; Max BP = blood pressure at maximal stress (mmHg); Max HR = maximal heart rate (beats/min); Post = posterior; PVCs = premature ventricular complexes; Sept = septum; SPECT = site of fixed defect on single-photon emission computed tomography; ST = electrocardiographic changes; VTs = sustained ventricular tachycardia; VTns = nonsustained ventricular tachycardia.

Table 1 - Demographic, Electrocardiographic, Echocardiographic and Scintigraphic Results

at peak stress while an improvement of wall motion (including wall thickening) of a severely hypokinetic or akinetic segment during low dose dobutamine is considered a marker of residual viable myocardium (5,6). Therefore, the evaluation of dobutamine stress echocardiography in two phases, at low and high doses, allows a more complete and comprehensive evaluation particularly in patients with left ventricular dysfunction, who represent an increasing proportion of patients in our daily practice.

The interpretation of stress echocardiography for the detection of myocardial ischemia is easiest in patients with normal or moderate hypokinesia on the resting echo, but is increasingly difficult in patients with previous myocardial infarction and severe hypokinesia or akinesia at rest. The main question in these cases is if the worsening of akinesis, becoming dyskinesis during stress, represents myocardial ischemia or is mainly a mechanical phenomenon due to a systolic outward bulging secondary to a hyperdynamic contraction of the remaining myocardium. The concepts of stunned and hibernating myocardium, which may be viable but not contractile at rest (5,6), make this an important issue.

The main finding of our study, in which we used a simultaneous perfusion scintigraphy as standard for comparison with stress echo, is that the scintigraphic equivalent of an akinetic segment becoming dyskinetic during peak stress, without an improvement of wall thickening during low-dose dobutamine is that of a severe and "fixed" perfusion defect, consistent with the presence of an infarcted tissue without significant ischemia in that territory. If we accept the perfusion scintigraphy as an adequate "gold standard" for the diagnosis of myocardial ischemia, these data suggest that the assessment of dobutamine stress echocardiography in two stages is useful to clarify this stress echocardiographic pattern.

We acknowledge that this study would be more complete if we had included patients in whom an improvement of wall thickening occurred during low dose dobutamine, to assess the frequency of stress induced ischemia in these patients. Another potential limitation of the study is that the radiotracer used was different in different patients, since technitium-99m isonitrile was used in 16 patients and thallium in 4 cases. It is very unlikely that the conclusions of the study were influenced by this methodological problem, since in previous studies little disagreement has been found between stress/rest technetium-99m isonitrile and thallium studies for the detection of myocardial ischemia (13).

In summary, by a combined dobutamine stress echo and perfusion scintigraphy we conclude that in the event of no improvement of wall

thickening at low-dose dobutamine, the echocardiographic pattern of an akinetic segment at rest becoming dyskinetic during peak stress does not represent myocardial ischemia and is probably related to a mechanical phenomenon due to a hypercontraction of the surrounding myocardium.

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CHAPTER IX

POTENTIAL AND LIMITATIONS OF Tc-99m SESTAMIBI SCINTIGRAP-HY FOR THE DIAGNOSIS OF MYOCARDIAL VIABILITY *

Summary

Sestamibi is a Tc labeled radiotracer particularly suitable for myocardial perfusion studies, providing similar information to thallium scintigraphy for the diagnosis of coronary artery disease, but having the advantage of better imaging properties due to a higher energy properties than thallium. This is particular relevant when SPECT imaging is considered. The role os sestamibi for the diagnosis of coronary artery disease is well accepted, while it is controversial for the assessment of myocardial viability. The myocardial uptake of sestamibi is partially passively related to the myocardial flow, but it also related to the metabolic cellular activity, being proportional to the electrochemical gradient generated at cell membrane level.

Clinical studies reported by others and results from our own institution will be described both in the setting of a recent myocardial infarction (myocardial stunning) and of long standing left ventricular dysfunction (hibernating myocardium) concordantly suggest that sestamibi underestimates myocardial viability, compared to the accepted standards of thallium (rest-redistribution or stress-reinjection protocols), 18-F FDG PET and also in the prediction of left ventricular functional recovery after revascularisation. However, the data available, particularly after revascularisation, are very limited. Furthermore, according to new promising results, the role of sestamibi in the setting of myocardial viability has potential for improvement, if the resting injection will be performed during nitrates. It is also foreseen that the combined use of sestamibi perfusion/wall motion scan (first pass and/or gated perfusion studies) and the developement of new softwares for attenuation correction might improve the results in the setting of myocardial viability.

* Cornel JH., Arnese M., Forster T., Postma-Tjoa, Reijs AEM, Fioretti PM, Herz 1994; 19:19-27.

Introductiom

Sestamibi is a Tc labeled myocardial perfusion agent, providing similar information to thallium scintigraphy for the diagnosis of coronary artery disease15, but having the advantage of having better imaging properties than thallium, particularly when SPECT imaging is considered16. The major draw-back of thallium for imaging are its low X-ray energy (68 to 80 keV) and its long physical half life (73 hours). In contrast, the X-ray energy of sestamibi is higher (141 keV) and its physical half life shorter (6 hours). An other difference between thallium and sestamibi is the lower first pass extraction of sestamibi (40% vs 80%), which is compensated by the slow myocardial clearance of sestamibi (16, 32). This last property allows the decoupling between the injection of the tracer and imaging, which can be advantageous in several clinical conditions, like acute myocardial infarction or unstable angina.

While use of sestamibi for myocardial perfusion is well accepted, its role for assessing myocardial viability is still controversial (3, 7, 16).

Properties of sestamibi and experimental results.

Sestamibi is a positively charged technetium complex, surrounded by 6 isonitrile groups (16). Its tissue uptake is parallel to myocardial flow, with the exception of high flows, at which thallium uptake is better (21, 30). However, the uptake of sestamibi at cellular level is also proportional to the electrochemical gradient generated at cell membrane level (26). Therefore, the uptake myocardial uptake of sestamibi, being dependant on coronary flow and cell membrane integrity (15) reflects myocardial perfusion and also, in some way myocardial viability.

On the basis of these experiments, it seems expectable that sestamibi would be comparable to thallium for the detection of viable, stunned myocardium, in which the myocardial perfusion has been restored after the ischemic episode. In contrast, thallium, due to its properties of redistributing seems more suitable than sestamibi in the setting of hibernating myocardium, due to the chronic low-flow (3). In this condition, a resting sestamibi scan are expected to show a perfusion defect, possibly underestimating the presence of viable myocardium. However, we should remember that it is very likely that in the clinical setting stunned and hibernating myocardium coexist and constitute a dynamic condition. Therefore a distinction between stunning and hibernating is more theoretical than real in the patients that we daily deal with.

Clinical applications of sestamibi for the study of viability in patients with acute or recent myocardial infarction.

Due to its unique physical properties, sestamibi allows an uncoupling between the injection of the tracer and imaging, allowing to acquire the images up to a few hours after the injection which still will reasonably reflect the perfusion conditions at the moment of the injection. This has been shown to be particularly interesting in the setting of patients with evolving infarction, in which serial resting perfusion studies have been done in the acute phase, before thrombolysis, and a few days later (12, 28, 34). In this way, measuring the recovery of perfusion, some information on the extent of myocardial salvage could be obtained. Importantly, it has been shown that this approach has the potential to assess not only the initial risk zone, but also the success of reperfusion, in terms of recanalisation (34) and the spontaneous recovery of left ventricular regional wall motion at one month after the acute phase (28). These data strongly indicate that sestamibi does not simply provide information on myocardial perfusion, but also on myocardial viability.

In line with these observations, Gibbons and co (13) have used sestamibi for assessing myocardial salvage in a trial comparing immediate primary angioplasty with the administration of an intravenous thrombolyic agent followed by a conservative approach. Although sestamibi SPECT imaging during the first few days after acute myocardial infarction is a very attractive method, it has been suggested that it may be a not ideal one for assessing myocardial viability in this setting, since a considerable amount of hibernating myocardium can be present at hospital discharge and sestamibi has been shown to underestimates the extent of hibernating myocardium (27).

Also, the optimal timing for assessing myocardial perfusion and/or viability after a recent infarction is not settled. Pellikka an co (23) have demonstrated in 25 consecutive patients treated with thrombolysis that there is a sustained improvement of sestamibi uptake by an additional 10% from 18-48 hours to 6-14 days after the acute phase. An example of a spontaneous improvement of sestamibi uptake from the second to the 21th day after an acute myocardial infarction treated with thrombolysis who came to our observation, is reported in figure 1. This example shows how myocardial "viability" could be underestimated if the perfusion study is performed "early" after the acute event.

More recently, still unpublished data by Marcassa and co (17) , based on a study in 52 patients, show that the uptake of sestamibi may spontaneously improve even in a later stage, from 6 weeks to 6

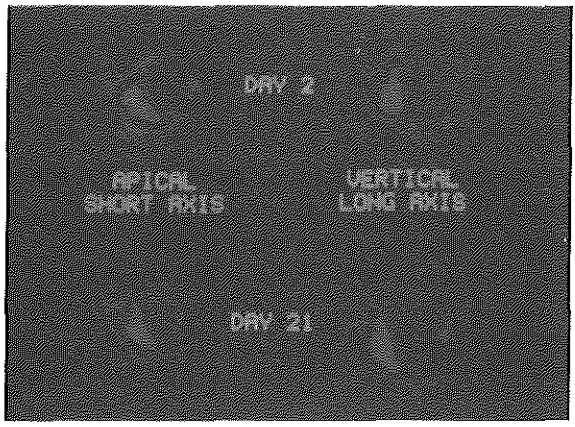

Figure 1a

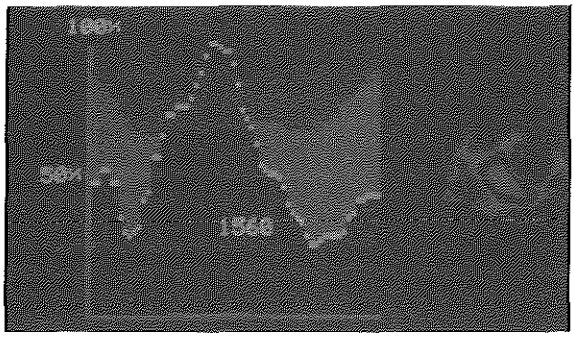

Figure 1b - (apical short axis, day 2)

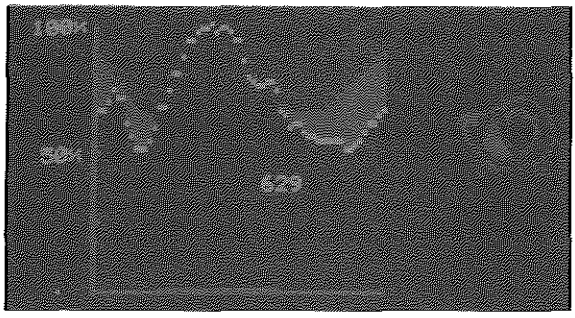

Figure 1c - (Apical short axis, day 21)

Figure 1a to 1c - Spontaneous improvement of sestamibi uptake from the early (two days) to a later (21 days) stage after an acute anterior infarction treated with thrombolysis. In a) the serial changes in apical short axis and vertical long axis slices are shown. It is obvious that a spontaneous substantial improvement of myocardial perfusion took place in the infarcted area (anterolateral). In b) and c) the same short axis slices are depicted, combined whit the correspondent circumpherential profile analysis, showing a decrease of the area below the normal limits (from 1560 to 629 units), consistent with the reduction of the perfusion defect on visual assessment.

months after an acute myocardial infarction. This study, in which quantitative analysis was applied, found an improvement of the extent of sestamibi uptake by 21% on average during this time span. This improvement was accompanied by a parallel improvement of left ventricular ejection fraction.

As far as we are aware of, there are no head to head comparisons between sestamibi and thallium scintigraphy in patients with recent myocardial infarction for assessing residual viability. Therefore, we extended our previous observations in 21 consecutive patients with a recent (7-10 days) Q-myocardial infarction (9) who were studied with sequential resting SPECT sestamibi and rest-4 hour redistribution 201-Thallium SPECT. Eleven patients had an anterior infarction. The aim of this study was to compare the extent and the severity of the perfusion defect with the 2 different tracers. Our hypothesis was that, if thallium uptake reflected myocardial viability better more sestamibi, the thallium defects would be smaller compared to the sestamibi defects.

We performed a quantitative assessment of the perfusion defects by circumferential profile analysis of 6 standardized short axis slices, compared to the results in normal subjects. The profiles were defined within the automatically detected endo and epicardial boundaries. The normal limits were separately defined for sestamibi and thallium as within 2 standard deviations of the mean values of normal subjects. The perfusion defects were calculated by summing the areas in the 6 short axis slices which were below the lower limit of the normal subjects.

The results, summarized in table 1 and in figures 1 ad 2 e 3, indicate that indeed the severity of sestamibi defect was systematically larger compared to that of thallium, independent of the location of the infarction. This suggest that the thallium is a more proper tracer for viability in the setting of recent myocardial infarction, while sestamibi is more related to myocardial perfusion and underestimates viability.

Sestamibi at rest	2977 ± 1904*
Thallium rest, post-injection	1896 ± 1169
Thallium, four hour redistribution	1820 ± 1211

Table 1 - Severity of perfusion defects (unitless, mean ± SD) of sestamibi and resting Thallium (post-injection and four hour redistribution) SPECT in 21 patients with a recent Q-myocardial infarction.

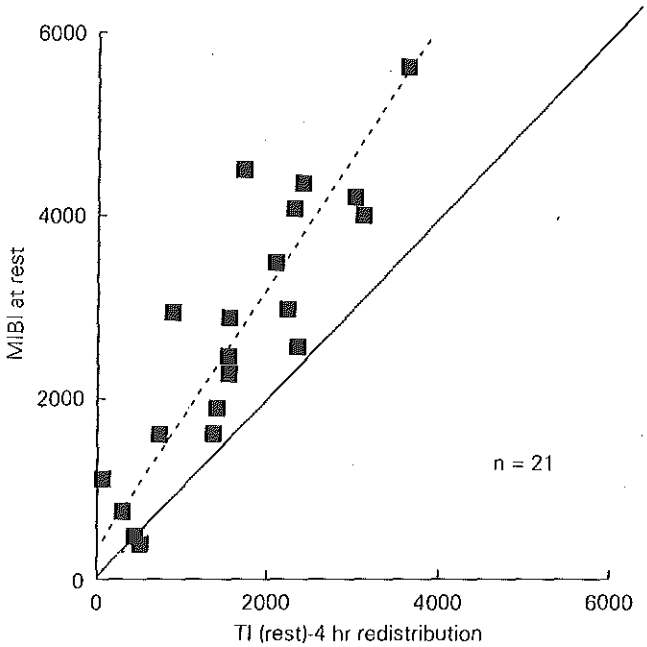

Figure 2 - Scatter diagram comparing the quantitative analysis of the perfusion defect from (rest)-four-hour redistribution thallium and resting sestamibi SPECT imaging in 21 patients with a recent myocardial infarction. The dotted line is the regression line and the continuous line is the identity line. Although there is a reasonable correlation between the two methods, the sestamibi defect was systematically larger than the thallium defect.

Figure 3a

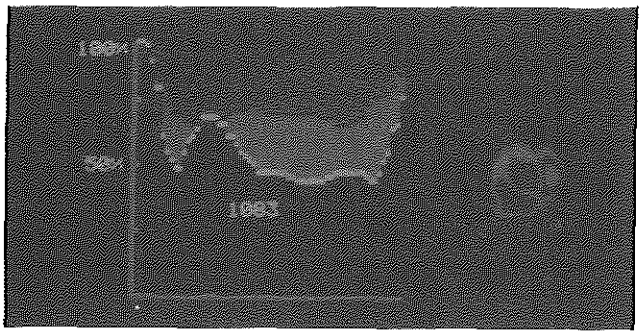

Figure 3b

Figure 3a and 3b - Matched apical short-axis slices of thallium rest-four-hour redistribution SPECT (a) and sestamibi SPECT (b) in a patient with a recent (ten days) large anterior infarction. As by visual assessment, and by analysis of the circumferential profiles, the smallest perfusion defect was observed on the delayed thallium imaging, while the largest was present on sestamibi imaging.

Clinical applications of sestamibi for assessing myocardial viability in patients with coronary artery disease and chronic left ventricular dysfunction.

Some recent studies have been addressed recently in a direct or indirect way to assess the merit of sestamibi in the setting of chronic left ventricular dysfunction, where a correct identification of the distribution of scarred, stunned and hibernating myocardium may be crucial for a proper indication to revascularization procedures.

There are 2 kind of data available: the first are comparative studies between sestamibi and other "standard" viability tracers, like thallium (5, 8, 33) or F-18 FDG PET (1, 2,) the second kind is that of studies using the improvement of left ventricular wall motion after revascularization as a standard for viability (18, 19, 20).

Comparison between sestamibi and thallium. The 2 tracers have been compared by different authors using different protocols and all studies have very similar conclusions, that sestamibi overestimates necrosis compared to thallium.

Cuocolo and co (5) compared exercise-redistribution-reinjection thallium with exercise-rest sestamibi (2 day protocol) planar imaging in 20 patients with proven coronary disease and left ventricular dysfunction (average ejection fraction of 30%). These authors found 122 regions with irreversible thallium defects at redistribution. 57/ 122 of these regions (47%) had a filling-in after thallium reinjection.

In contrast, only 22/122 regions had a reversible defect on exercise-rest sestamibi.

Dondi and co (8) and Taylor and co (33) compared exercise-rest sestamibi SPECT with rest-redistribution thallium (3) hour (8) and (24) hour (33) in patients with left ventricular dysfunction, and they also found a greater incidence of reversible thallium defects with thallium compared to stress-rest sestamibi. In particular, Taylor and co (33) found that in 167 sestamibi severe fixed defects, 87(57%) showed a late (24 hour) thallium redistribution, suggesting the presence of viable myocardium undetected by sestamibi.

In order to compare the size of the perfusion defect with thallium and sestamibi, we have recently studied 26 patients with chronic left ventricular dysfunction with sequential high dose dobutamine (up to 40 μg/kg/min)-reinjection thallium (10) and resting sestamibi SPECT imaging (unpublished data). The SPECT imaging were quantitatively analyzed, as described in the previous section of the present article. Similarly to the comparative study in patients with a recent infarction, the resting sestamibi defects were significantly larger than the thallium reinjection defects (3777 ± 1599 vs 2541 ± 1274, $p<0.05$) (figure 4). This reinforces the concept that resting sestamibi may underestimate the extent of residual myocardial viability.

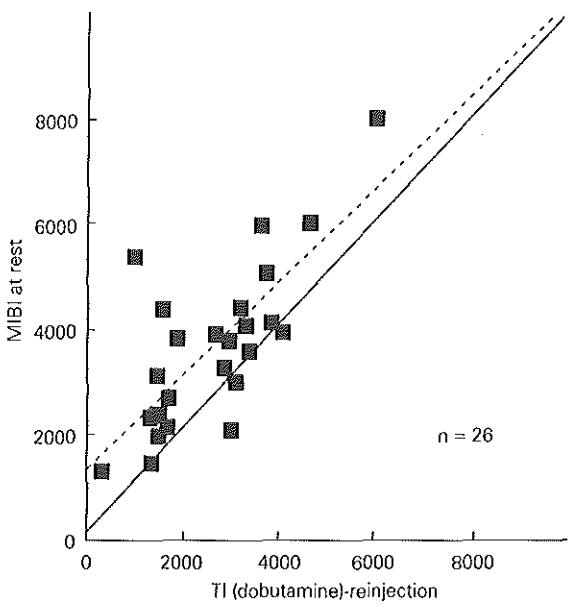

Figure 4 - Scatter diagram for comparison between the severity of perfusion defect from resting sestamibi and (dobutamine)-reinjection thallium SPECT in 26 patients with an old myocardial infarction. The continuous line represents the identity line and the dotted line the regression line. The data show a reasonable correlation between the two methods, with a systematic overestimation of the perfusion defect by sestamibi.

Different protocols have been used in the previous studies for comparison, however it has been recently been demonstrated that only trivial differences for assessing viability are present between stress-redistribution-reinjection and rest-redistribution thallium protocols (6). Therefore it likely that the concordant results of all the different studies are consistent with similar conclusions.

Comparison between 18-F FDG PET and sestamibi. Recently Altehoefer and co published a study comparing resting sestamibi SPECT with 18-F FDG PET for assessing viability in 46 patients with chronic coronary artery disease and regional wall motion abnormalities (1), and recently extended his observations to a larger group of 111 patients (2). The important findings of these authors (figure 5) is that in a substantial proportion of patients with a "severe" (> 50%) sestamibi uptake defect there was an FDG uptake, marker of the presence of viability. It is concluded by the authors that FDG uptake provides additional informations potentially useful for clinical decisions in patients with severe sestamibi uptake defects who are considered for revascularization procedures.

These data are in agreement with the comparative data with thallium previously discussed.

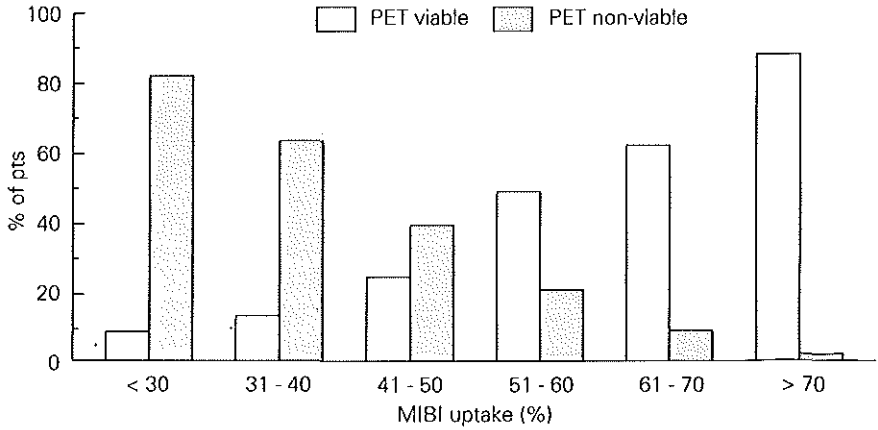

Figure 5 - Results of the comparison between resting sestamibi and 18-F FDG PET in 111 patients with chronic coronary artery disease and wall motion abnormalities at rest, from Altehoefer et al. [2]. From the data it clearly appears that the sestamibi uptake underestimates the extent of viable myocardium (especially between 31 and 70% of sestamibi uptake defects), when 18-F FDG PET is considered the "golden standard".

Comparison between stress echocardiography and sestamibi. Stress echocardiography is emerging as a new, potentially useful tool for assessing myocardial viability, particularly in the setting of stunned myocardium in patients with recent myocardial infarction (22, 24, 25, 29). However, few data on the value of stress echo are available in hibernating myocardium (4) or comparing stress echo to sestamibi (18).

Therefore, we found of interest to briefly describe our comparative results (unpublished data) for assessing myocardial viability between simultaneous high-dose dobutamine-rest sestamibi SPECT and low-dose dobutamine echocardiography in 83 consecutive patients with an old myocardial infarction.

The criteria for assessing echo viability in dyssynergic regions was an improvement of wall thickening, by visual inspection, during the infusion of a low-dose dobutamine (5 or, if no change was observed, 10 μg/kg/min during steps of 3 minutes). The criteria for defining sestamibi viability were the presence of a normal perfusion, of a (partially)transient or fixed but moderate defect during high-dose dobutamine (up to 40 μg/kg/min)-rest sestamibi SPECT imaging. The severity of the defects were assessed visually and with the assistence of a circumferential profiles analysis of the short axis slices. The agreement between echo and sestamibi viability was assessed in six matched left ventricular regions.

The results on the agreement between echo and sestamibi are reported in table 2 and in figure 6. As we can see the agreement was on average poor, since sestamibi detected more frequently regions with viable tissue compared with low-dose dobutamine echo. The discrepancy was greatest in the 68 akinetic regions, of which 37 (54%) were sestamibi viable but only 13 (19%) were echo viable. Since we do not have the results on wall motion changes after revascularization in these patients, it is impossible to say which is the clinical relevance of these results. However these data would suggest that low-dose dobutamine echo underestimates the presence of hibernating myocardium. Clearly, more research is needed at this regard, since the data available so far are not sufficient being based on very small series of patients (4).

Studies with sestamibi before and after coronary revascularization. The number of studies to assess the value of sestamibi to predict the improvement of regional wall motion after revascualrization is very limited (18, 19, 20, 29). The results of the studies using resting sestamibi (18, 19, 20) indicate, although in small number of patients, that sestamibi has a relatively poor predictive value. In particular, Maublant and co (20) have observed that in 9 segments with a severe sestamibi defect wall motion improved after revascularization in (8).

Echo	No of LV segmets	MIBI viable	MIBI non viable
Normal WM	328	325	3
Hypokinesis +	73	67	6
Akinesis +	13	10	3
Hypokinesis -	29	24	5
Akinesis -	55	27	28

+ = improvement of wall thickening during low-dose dobutamine;
- = no improvement of wall thickening during low-dose dobutamine;
WM = wall motion.

Table 2 - Regional agreement for viability between sestamibi (high dose dobutamine-rest) and low-dose echocardiography, in 83 patients (six regions for each patient) with myocardial infarction.

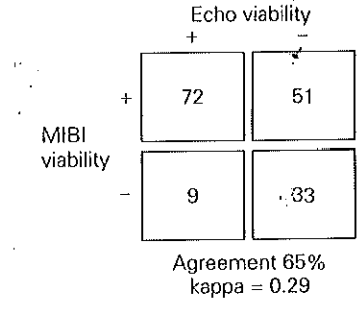

Figure 6 - Two by two table comparing the agreement between echo and sestamibi viability in dyssynergic (hypo or akinetic) regions on resting echocardiogram. The kappa value of 0.29 indicates a significant disagreement between the two methods. In particular, it appears that sestamibi detected more viable regions tham low-dose dobutamine echo.

Marzullo and co (18, 19) studied 14 patients before and 11 weeks after PTCA with resting sestamibi, rest-redistribution thallium and low-dose dobutamine. These authors also found that ther was a trend indicating that sestamibi had lower sensitivity and specificity compared to delayed thallium imaging.

In contrast, encouraging results for sestamibi in the same setting (before and after revascularization) were found if the resting injection of sestamibi was performed during the infusion of nitrates (29). In this way, in a study based on 20 patients, the results of sestamibi were comparable to those of rest-redistribution thallium. This approach, is particularly interesting and consistent with previous work by Galli and co with sestamibi (11) and by Zuo-Xiang and co (35) with thallium reinjection SPECT.

Conclusion

99m Tc sestamibi is a very valuable myocardial tracer for perfusion studies, but from the data so far available it seems less suitable than thallium for assessing myocardial viability, since it tends to overestimate the extent of myocardial necrosis and/or fibrosis.

However, also because of its superior imaging properties, the value of sestamibi for myocardial viability should be further investigated. The potential improvements could be achieved in different ways: with the systematic administration of nitrates before the resting injection, repeating a delayed imaging (a small delayed redistribution has been described (32), combining perfusion and wall motion studies (first pass and/or gated imaging). Finally, the new methods for attenuation correction with transmission scan 14 will certainly reduce the artifacts, particularly the the false perfusion defects in the left ventricular posterior wall.

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CHAPTER X

PREDICTION OF IMPROVEMENT OF REGIONAL LEFT VENTRICULAR FUNCTION AFTER SURGICAL REVASCULARIZATION: A COMPARISON OF LOW-DOSE DOBUTAMINE ECHOCARDIOGRAPHY WITH 201-TL SPECT*

Abstract

Background. Although both Thallium-201 (TL) scintigraphy and low-dose dobutamine echocardiography (LDDE) have been proposed as effective methods for the assessment of myocardial viability, their relative efficacies are unknown. The aim of the present study was to compare the two imaging techniques in the prediction of improvement of regional left ventricular function after surgical revascularization.

Methods. Thirty-eight patients with severe chronic left ventricular (LV) dysfunction (ejection fraction less than or equal to 40%, one or more akinetic (Ak) or severely hypokinetic (SH) segment on resting echocardiogram) who underwent uncomplicated coronary artery bypass surgery were studied with simultaneous dobutamine stress echocardiography and post-stress reinjection TL single photon emission computed tomography (SPECT) before surgery. The Ak or SH segments were considered viable by LDDE when wall thickening improved during the infusion of 10 μg/kg/min of dobutamine. Scintigraphic definition of viability was the presence of normal TL uptake, totally reversible defect, partially reversible defect or moderately severe fixed defect. The postoperative improvement of dyssynergic segments was determined by a rest echocardiogram three months after surgery.

Results. Out of 608 left ventricular segments, 169 were classified as Ak and 51 as SH on resting preoperative echocardiogram. Of these, 170 were successfully revascularized. Wall motion during LDDE improved in 33 severely dyssynergic segments and was more frequent in SH than in Ak segments (19/44 vs 14/126, $p < 0.0001$). Viability

* Arnese M, Cornel JH, Salustri A, Maat APWM, Elhendy A, Reijs AEM, Ten Cate FJ, Keane D, Balk AHMM, JRTC Roelandt, Fioretti PM. Circulation 1995;91:2748-2752.

was detected by TL SPECT criteria in 103 SH or Ak segments. Thirty-two out of the 33 segments LDDE responder were judged viable on TL SPECT, while TL viability was detected also in 71/137 segments LDDE non responders. The sensitivity and the specificity for the prediction of postoperative improvement of segmental wall motion were 74% (95% C.I. 67%-81%) and 95% (92%-98%) by LDDE, 89% (84%-94%) and 48% (40%-56%) by TL SPECT respectively. Positive predictive value of LDDE was higher than that of TL SPECT (85%, C.I. 80%-90%, vs 33%, C.I. 26%-40%).

Thirty-six patients had angina before and only one had angina three months after revascularization. High-dose dobutamine echocardiography demonstrated significant reduction of stress induced ischemia (new of worsening of pre-existing wall motion abnormalities) after surgery (from 163 to 23 left ventricular segments).

Conclusions. In patients with severe chronic LV dysfunction, LDDE is a good predictor of the improvement of dyssynergic segments after revascularization. Because TL SPECT overestimates the probability of postoperative improvement of dyssynergic segments, LDDE should be the preferred imaging technique for pre-operative assessment of these patients.

Introduction

Coronary artery bypass grafting can improve regional and global ventricular performance and the functional status of patients with chronic left ventricular dysfunction (1). The concepts of stunned and hibernating myocardium have been advocated to explain such improvement (2,3). Reliable pre-operative prediction of patients in whom regional and/or global left ventricular dysfunction will improve after revascularization would present several clinical advantages. These potential advantages would include a) the appropriate referral for cardiac surgery of patients who are currently considered to be unsuitable for revascularization, b) the referral of patients for revascularization who would at present only be considered for cardiac transplantation, and c) the avoidance of cardiac surgery in patients in whom revascularization would result in no functional benefit (but would only carry significant risk of perioperative morbidity and mortality).

Both TL SPECT (2-5) and, more recently, low-dose dobutamine echocardiography (LDDE) have been proposed as effective techniques for the evaluation of myocardial viability (6-11). While LDDE is more widely available, it is unknown whether its efficacy and reliability equals that of TL SPECT which is more established in this role (2-5).

To determine the relative merits of the two imaging techniques, we compared TL SPECT and LDDE in the prediction of functional recovery in 38 patients with left ventricular dysfunction undergoing coronary artery bypass surgery. Post-operative resting echocardiography at three months was used to determine left ventricular improvement.

Methods

Study population. Fourty-three patients with stable left ventricular dysfunction undergoing coronary artery bypass surgery fulfilled the study inclusion criteria:

- ejection fraction of £ 40% on contrast ventriculography;
- history of previous (> 3 months old) myocardial infarction;
- one or more akinetic (Ak) or severely hypokinetic (SH) segments on pre-operative resting echocardiography (16-segment left ventricular model);
- absence of recent episodes of unstable angina;
- absence of significant (> 50%) left main stem stenosis;
- absence of (hemodynamically) significant valvular disease.

Five patients were withdrawn from the study on account of peri-operative myocardial infarction (3 patients), resection of all dyssynergic segments (1 patient), inability to graft any of the Ak of SH segments (1 patient). Thirty-eight patients were finally included in the study. The mean age of the patients was 59 years (range 36-73) and 26 were male. All patients were symptomatic, 36 had angina pectoris and 20 had dyspnea on effort. Mean angiographic left ventricular ejection fraction was 31% (range 18-40%). Single vessel disease, defined as diameter stenosis of a major coronary artery > 50%, was present in three patients, 16 patients had two vessel disease, and 19 patients had three-vessel disease. Four patients had undergone previous coronary artery bypass surgery. Four patients were on beta-blockers during the preoperative diagnostic work-up.

Dobutamine stress echocardiography. The dobutamine stress test was performed as follows. A two-dimensional transthoracic echocardiogram in standard views and a 12-lead electrocardiogram (ECG) were recorded at rest. Dobutamine was infused through an antecubital vein at doses of 5 and 10 µg/kg/min, for 3 minutes at each dose. Subsequently, other 3 steps from 20 to 40 µg/Kg/min (3 minutes each) were added. Finally, atropine (up to 1 mg) was injected in the negative cases where 85% of the maximal heart rate rate was not reached (12). Echocardiogram was monitored during the test, and the last minute of each stage was recorded on video tape. The echocardiographic images were also digitized (on optical disk -

Vingmed CFM 800, or on floppy disk - Esaote Biomedica SIM 7000) and displayed side by side in quad-screen format to facilitate the comparison of rest and dobutamine images with subsequent post-operative images. A 3-lead ECG was monitored continuously and a 12-lead ECG was recorded every minute. Blood pressure was measured by sphygmomanometer at each 3 minute stage.

Post-operative echocardiography. To assess the functional outcome of the dyssynergic segments, resting two-dimensional echocardiograms were obtained in all patients 3 months after cardiac surgery. In addition, high-dose dobutamine/atropine stress echocardiography was obtained in 32 patients.

Analysis of pre- and post-operative echocardiograms. The interpretation of echocardiograms was performed by two experienced observers, blinded to the clinical, angiographic and previous echocardiographic results of the individual patients. In a subset of 11 patients (176 segments) the inter- and intra-observer variability of the classification of resting wall motion and the response to LDDE was assessed as well. The assessment was based on both the digitized images displayed in a quad-screen format and by reviewing the images recorded on the video tape. The assessment was semi-quantitative, and a 16-segment model (13) was used. The wall motion, including wall thickening, of every segment was scored with a 5-point scoring system, where 1=normal wall motion and thickening, 2=moderately hypokinetic, 3=severely kypokinetic, 4=akinetic, and 5=dyskinetic. We defined a segment as severely hypokinetic in the presence of minimal wall thickening with a limited inward motion of < 2 mm; as akinetic in the absence of systolic wall motion and thickening and also, whenever possible, confirmed by M-mode tracing; as dyskinetic in the presence of systolic outward wall motion with thinning.

Wall thickening was primarily utilized for the classification of wall motion, preventing the problem of post-operative paradoxical septal motion. Additionally, in order to reduce the confounding effect of tethering from adjacent segments, segmental wall thickening was analysed frame by frame during the first half of systole. Myocardial viability was judged to be present in a dyssynergic (either Ak or SH) segment when wall motion improved during the infusion of low-dose dobutamine by at least one point of the scoring system. Thus, a severe hypokinesis becoming moderately hypokinetic or systolic myocardial thickening becoming apparent in a previously akinetic segment were considered as markers of viability. Myocardial ischemia was judged to be present in case of worsening ≥ 1 of the segmental score. Akinetic and dyskinetic segments were not evaluated for this purpose.

Follow-up echocardiograms were compared with the corresponding pre-operative resting images. For each segment,

improvement of function was defined as a decrease of one or more grades. Moreover, we utilized the pre- and post- operative wall motion score index (WMSI) to evaluate the effect of revascularization on global LV function. WMSI was defined as the sum of the degrees of each segment divided by the total number of segments analysed.

Thallium SPECT imaging. Briefly, as previously described (14-16) TL (2mCi) was injected intravenously 1 minute before the termination of the infusion of high-dose dobutamine (up to 40 mcg/kg/min, with the addition of atropine if there were no signs of ischemia and if the 85% of the maximal heart rate was not reached). The acquisition of the post-stress SPECT imaging was started within 10 minutes after the interruption of the dobutamine infusion. All images were acquired by a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp., Iselin, N.J.) and a low energy, all purpose collimator. Thirty-two projections were obtained, from left posterior oblique to right anterior oblique, with an acquisition time of 45 seconds for each projection. A Gamma 11 computer system was used to process the tomographic data. Four hours after the stress imaging, a second acquisition was performed 20 minutes following the reinjection of 1 mCi of TL.

As previously described (15,16), the interpretation of the images was based on 6 short axis slices, 3 longitudinal and 3 transverse long axis slices (both stress and post-reinjection). The analysis was performed visually with the assistance of quantitative measurement (circumferential profiles). The same 16-segment model used for interpretation of the echocardiograms was applied for the interpretation of the SPECT images. Scintigraphic images from the short axis and the long axis views were matched with the echocardiographic images. Each defect was classified as fixed, partially reversible, or totally reversible. A myocardial segment was considered as non-viable in the presence of a severe irreversible defect. A defect was classified as severe if the TL uptake of a segment was less than 50% of the uptake of the "normal" segments on the quantitative circumferential profile analysis and if it was consistent with a severe visually assessed defect. Scintigraphic definition of viability was based on the presence of normal TL uptake, totally reversible defect, partially reversible defect, or moderately severe fixed defect.

Statistical analysis. Continuous data are expressed as mean ± standard deviation. Univariate analysis for categorial variables was performed using the chi-square test with Yate's correction. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. Sensitivity, specificity and positive and negative predictive values were based upon their standard definitions and are reported with the corresponding 95% confidence intervals

(C.I.). The inter- and intra-observer variability of regional wall motion pattern was assessed as % agreement and kappa value.

Results

Pre-operative data. Out of a total number of 608 left ventricular segments, 169 were classified as Ak and 51 as SH. Fourty-three Ak segments were excluded from the postoperative evaluation on account of aneurysmectomy (n=41), or because they were not grafted (n=2). Out of the 51 SH segments, 7 were excluded from the post-operative evaluation on account of aneurysmectomy (n=3) or because they were not graftable (n=4).

Low-Dose Dobutamine Echocardiography. Only 14 out of the 126 Ak segments which could be successfully revascularized, showed the presence of wall thickening during low-dose dobutamine on preoperative echocardiogram. These 14 Ak segments were detected in 8 patients.

Wall thickening improved during the infusion of dobutamine in 19 of the 44 SH segments. These 19 segments were present in 9 patients. Thus, viability was detected more frequently in severely hypokinetic than in akinetic segments ($p<0.0001$).

The inter- and intra-observer concordance of resting wall motion analysis were 84% (kappa 0.79) and 87% (kappa 0.82) respectively. The inter- and the intra-observer concordance of the response of wall motion during LDDE were excellent as well by 92% (kappa 0.84) and 94% (kappa 0.86) respectively.

High-dose dobutamine echocardiography. At peak stress, new or worsening of pre-existing wall motion abnormalities were detected in 163 out of 576 segments, in 32 out of the 36 patients. Angina during the test occurred in 28 patients.

Thallium SPECT. TL SPECT imaging indicated the presence of viable myocardium in 49/112 Ak regions not responding and in 14/14 Ak regions responding to dobutamine, in 22/25 SH regions not responding and in 18/19 SH regions responding to dobutamine (Table I). From these data it is clear that TL SPECT indicates viable myocardium more frequently than LDDE ($p<0.001$). Figure 1 displays the distribution of perfusion patterns by TL SPECT according to the different LDDE results.

Postoperative clinical and echocardiographic data. At 3 months post-operatively, only one patient had angina and 10 patients still complained of dyspnea on effort.

LDDE patterns		Thallium viability	Postoperative improvement
Ak -	112	49	9
Ak +	14	14	13
SH -	25	22	1
SH +	19	18	15

Abbreviations: Ak: akinetic segments; LDDE = low-dose dobutamine echocardiography; SH: severely hypokinetic segments; +/- = improvement/no improvement of wall motion during low-dose dobutamine infusion.

Table 1 - Relationship between preoperative dobutamine echocardiographic results, viability on thallium SPECT and postoperative outcome of wall motion in severely dyssynergic segments.

Improvement of regional wall motion. Resting echocardiograms at three months post-operative follow-up revealed an improvement of wall motion in 38 (22%) of the 170 dyssynergic segments. The improvement was found in 22 (17%) out of the 126 Ak segments (to SH in 6 segments, to moderate hypokinesis in 13 segments, to normal in 3 segments) and in 16 (36%) out of the 44 SH segments (to normal in 8 segments, and to moderate hypokinesis in 8 segments) (p=0.02).

Reduction of dobutamine induced myocardial ischemia.

Out of 32 patients who underwent a high dose dobutamine stress test during follow-up, three had angina at peak stress. New or worsened wall motion abnormalities were detected in 10 patients, and in 23 out of 512 left ventricular segments.

Prediction of regional improvement. Post-operative improvement occurred in 28 of the 33 segments which improved during LDDE and in only 10 of 137 segments which did not improve (Table I). Of the segments judged to be viable by LDDE, a postoperative improvement occurred in 79% of SH and in 93% of Ak segments.

Thallium-201 SPECT detected the presence of viable myocardium in 32 of the 33 matched segments considered viable by LDDE. Despite the frequent indication of viability by TL SPECT in the Ak segments unresponsive to dobutamine (44%), improvement after surgery was found in only 8% of these segments. Similarly, wall thickening improved after revascularization in only 1 of the 25 SH regions unresponsive to dobutamine, despite signs of viability by TL SPECT in 22 of these 25 segments. Table II shows the predictive accury with

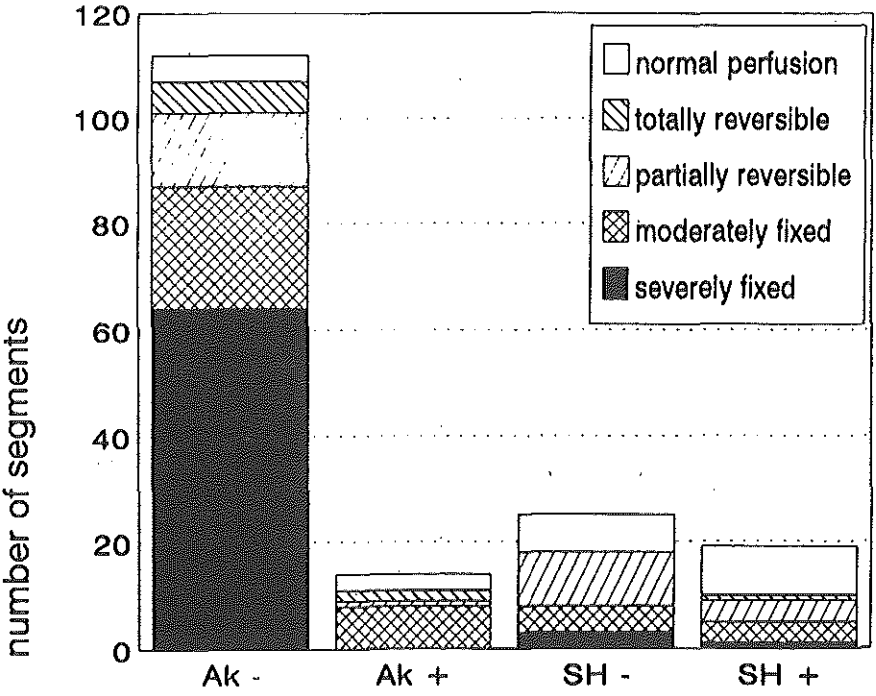

Figure 1 - Distribution of dobutamine/atropine-reinjection thallium-201 SPECT perfusion patterns in 4 predefined low-dose dobutamine echocardiographic patterns. Abbreviations: Ak = akinetic segment; SH = severel hypokinetic segment; - = non-viable; + = viable; fixed = fixed perfusion defect; reversible = reversible perfusion defect.

95% confidence intervals of the two methods for the post-operative improvement of SH and of AK segments.

Global left ventricular function. The WMSI revealed that there were no significant differences before and after coronary artery bypass surgery, neither in the subset in whom myocardial viability was predicted by LDDE (13 patients) (2.6 ± 0.5 vs 2.4 ± 0.4) nor in the entire study population (2.3 ± 0.5 vs 2.3 ± 0.5).

Coronary angiography. A routine coronary angiogram independent of the recurrence of symtoms was undertaken in 14 patients at 3 months follow-up. Sustained patency of the grafts to the Ak or SH segments was demonstrated in all of these patients.

Discussion

The functional assessment of hibernating myocardium and the presence of viability is clinically challenging (3) and of paramount importance for the selection of the most appropriate treatment for individual patients with chronic severe left ventricular dysfunction (1).

We prospectively studied a group of patients with severe chronic left ventricular dysfunction candidate for surgical revascularization in order 1) to assess the prevalence of regional improvement of Ak/SH segments after surgical revascularization, and 2) to evaluate the role of LDDE and TL SPECT for predicting such improvement. In addition, the reversibility of stress induced myocardial ischemia was also assessed by clinical judgement and high-dose dobutamine stress test.

In this series of patients, improvement of regional function after revascularization was found in 22% of Ak/SH segments. This value is lower than in other series (7,9-10), and might be related to the selection of patients with severely impaired LV function in a tertial referral center with an ongoing heart transplant program.

We have demonstrated that pre-operative LDDE is both a sensitive (28 out of 33 segments) as well as specific (127 out of 137 segements) predictor of post-operative outcome of regional myocardial function. The pattern of improvement of wall thickening in severely dyssynergic regions during the infusion of low dose dobutamine was found to be a reliable predictor of functional recovery of wall motion after successful and uncomplicated surgical revascularization, with a positive predictive value of 85% (C.I. 80-90), while the pattern of Ak or SH unresponsive to low-dose dobutamine is indicative of non-viable tissue and offers a negative predictive value of 93% (C.I 89-97).

Thallium SPECT (matched for echocardiographic segements) indicated the presence of viable myocardium more frequently than LDDE (103/170 vs 33/170). However, this imaging technique appears less suitable than LDDE to predict the post-operative improvement of regional wall motion in patients with severe LV dysfunction. In particular, the high prevalence of viability detected pre-operatively

Method	Sensitivity	Specificity	PPV	NPV
LDDE, %	74	95	85	93
95% C.I.	67 - 81	92 - 98	80 - 90	89 - 97
TL, %	89	48	33	94
95% C.I.	84 - 94	40 - 56	26 - 40	90 - 98

Abbreviations: C.I. = confidence Intervals; LDDE: low-dose dobutamine echocardiography; NPV: negative predictive value; PPV: positive predictive value; TL: Thallium SPECT

Table 2 - Diagnostic accuracy with 95% confidence intervals of low-dose dobutamine echocardiography and high-dose dobutamine-reinjection Thallium-201 SPECT for the prediction of postoperative improvement of wall motion in severely dyssynergic segments.

at TL SPECT and the low prevalence of post-operative functional improvement result in a low specificity and in a low positive predictive value (table II).

Overestimation of myocardial viability by perfusion scintigraphy may relate to several factors. Firstly, scintigraphy may detect islands of jeopardized vital myocardial cells of inadequate size to revert left ventricular dysfunction despite successful revascularization. Secondly, tethering by scar tissue may restrict the improvement in wall motion of adjacent viable segments. Thirdly, functional recovery may not have completed by three months (so called "embalmed myocardium") (17). Finally, since subendocardial layers play a major role in wall motion, a necrosis limited to the subendocardium may result in severe dyssynergy despite the presence of viable myocardium in the subepicardial layers (18).

In our study group, there was no significant post-operative improvement of global left ventricular function, however bypass surgery alleviated myocardial ischemia, since the number of patients with angina and the extent of stress induced ischemia was greatly reduced. This is consistent with the high post-operative patency rate of bypass coronary grafts, and confirmed the usefulness of dobutamine stress echocardiography for the assessment of stress induced myocardial ischemia after coronary revascularization (12).

Previous studies. While several studies have addressed the role of dobutamine echocardiography for the assessment of left ventricular functional recovery in patients with recent myocardial infarction (6-8,11,19), few data are available on its predictive value for post-revascularization functional improvement (9,10). In two previous studies on post-revascularization recovery, Marzullo et al (9) and Cigarroa et al (10) reported a higher incidence of wall thickening during low-dose dobutamine in AK regions (47% and 39% respectively, compared to 11% in our study). This discrepancy may relate to different methodologies (absence of sub classification for SH segments in their studies) and patient selection (inclusion in our study of patients with more severe and more longstanding ventricular dysfunction where stunned myocardium is less likely to be present). Considering the value of LDDE to predict the post-operative functional outcome, our findings are in agreement with the two previous reports.

Study limitations. The number of viable Ak and SH segments identified in our study was limited despite our analysis of a total of 608 segments both pre- and post- coronary bypass surgery. This, however, reflects our stringent inclusion criteria and our strict method of analysis (panel review with simultaneous, quad-screen format).

Secondly, we arbitrarely timed the outcome of dyssynergic segments 3 months after surgical revascularization. However, it cannot

be excluded that functional improvement can also occur later. Finally, this study was focused on the post-operative phase of regional wall motion. We are aware that the improvement in a limited area of myocardium can be clinically not relevant on global LV function. However, this was not the primary aim of the study.

Conclusion

Our observations in the setting of severe chronic left ventriculair dysfunction indicate that

1) wall thickening during low-dose dobutamine in akinetic segments is unfrequent, 2) responsiveness of akinetic and severe hypokinetic segments to low-dose dobutamine is both a specific and sensitive predictor of post-revascularization functional improvement, and 3) compared to LDDE, TL SPECT has an equivalent sensitivity for the prediction of post-operative myocardial functional improvement but a lower specificity. Thus, LDDE should be the preferred imaging technique for predicting the functional outcome of patients with severe left ventricular dysfunction under consideration for coronary artery bypass surgery.

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CHAPTER XI

IMPROVED CARDIAC RISK STRATIFICATION IN MAJOR VASCULAR SURGERY WITH DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY*

Abstract

Objectives. To optimize preoperative cardiac risk stratification in a large group of consecutive vascular surgery candidates by combining clinical risk assessment and semi-quantitative dobutamine-atropine stress echocardiography.

Background: Dobutamine-atropine stress echocardiography has been used for the prediction of perioperative cardiac risk in small group of patients scheduled for elective major vascular surgery, based on the presence or absence of stress-induced regional left ventricular wall motion abnormalities.

Methods: Clinical risk assessment and dobutamine-atropine stress echocardiography were performed in 300 consecutive patients presenting for major vascular surgery. The extent and severity of stress wall motion abnormalities and the heart rate at which they occurred, in addition to the presence of wall motion abnormalities at rest were assessed.

Results. The absence of clinical risk factors (angina, diabetes, Q waves on ECG, symptomatic ventricular tachyarrhythmia's, age >70 years) identified a low-risk group of 100 patients with one-percent cardiac event rate (unstable angina). Dobutamine-atropine stress echocardiography was positive in 72 patients. Twenty-seven perioperative cardiac events (5 cardiac deaths, 12 nonfatal infarctions and unstable angina pectoris in 10) occurred, all in patients with a positive stress test (positive predictive value 38%, negative predictive value 100%). The semi-quantitative assessment of the extent and severity of ischemia did not provide additional prognostic information in patients with a positive test. In contrast, the heart rate at which ischemia occurred defined a high-risk group with a low ischemic threshold [38 patients with 20 events (53%)] and an intermediate-risk group with a high ischemic threshold [34 patients, 7 events (21%)].

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All 5 patients with a fatal outcome and 8 of 12 with nonfatal myocardial infarction were in the high-risk group with a low ischemic threshold.

In conclusion: Clinical variables identify a 1/3 of patients having a very low-risk of perioperative complications of vascular surgery in whom further testing is redundant. In all other candidates, dobutamine-atropine stress echocardiography is a powerful tool which defines an intermediate-risk population, and a small very high-risk group. Risk stratification with a combination of clinical assessment and pharmacological stress echocardiography has the potential to facilitate clinical decision-making, and contains resources.

Introduction

Perioperative cardiac complications are a leading cause of morbidity and mortality in patients undergoing major vascular surgery(1-4). For example, elective resection of an abdominal aortic aneurysm is associated with an operative mortality rate of 3-10 %(2), with approximately 50% of deaths being cardiac in origin. Effective preoperative risk stratification has the potential to facilitate decision-making by enabling patients and physicians to better assess the risk-benefit ratio of proposed surgical procedures. Furthermore, unequivocal definition of a low-risk group would permit expeditious and cost-effective surgical management of those patients.

Several techniques for preoperative cardiac risk assessment have been advocated. These include clinical evaluation(5-7), exercise electrocardiography(8), ambulatory electrocardiography(9,10), radionuclide ventriculography(11), and dipyridamole-thallium scintigraphy(12-14). Of these, dipyridamole-thallium myocardial perfusion scintigraphy has been most widely advocated. However, recent studies have found that dipyridamole-thallium scintigraphy to have poor predictive power and suggest that its routine use may not have been justified(15).

More recently, pharmacologic stress echocardiography with dobutamine or dipyridamole has been proposed as an alternative to dipyridamole-thallium scintigraphy for risk assessment in vascular surgery candidates(16-21). This technique uses transthoracic echocardiography to detect ischemic left ventricular wall motion abnormalities induced by pharmacologic stress. Preliminary studies suggest that stress echocardiography is a safe(22) and sensitive technique for predicting perioperative cardiac events, which has excellent negative predictive power(16-21). However, these previous studies had limitations. First, most studies did not enrol patients consecutively, so a referral bias may have been present. Second, clinicians caring for the patients usually had access to test results, and this

may have altered management. In some studies, apparently high-risk patients underwent coronary angiography and/or myocardial revascularisation prior to vascular surgery. Third, relatively small number of patients were studied. Finally, test result were classified simply as positive or negative, without including information about the extent and severity of inducible ischemia, or the threshold heart rate at which ischemia developed. This later defect might explain the relatively low positive predictive power of stress echocardiography in some studies(16,17). We attempted to overcome this limitations by evaluating the predictive power of dobutamine-atropine stress echocardiography in a large group of consecutive patients, while blinding clinicians to test results. We also attempted to improve the predictive power of the test by employing a quantitative approach which utilizes more of the information available from the test. This work represents an extension of our previous consecutive 136 patients(21).

Methods

Patient characteristics: Three-hundred-and-two consecutive patients scheduled for elective major vascular surgery were studied during a three-year period from 1991 to 1994. All patients were judged not suitable to be assessed by exercise testing. A detailed history, physical examination and 12-lead electrocardiogram (ECG) were performed and Detsky's modification of Goldman cardiac risk index was calculated for each subject. Using the method of Eagle et al(13), the number of clinical risk factors (angina, diabetes requiring drug therapy, age >70 years, Q wave on ECG and history of ventricular ectopic activity requiring treatment) present in each subject were counted. Minimal additional preoperative testing or therapy was undertaken. Three patients underwent dipyridamole-thallium myocardial scintigraphy and none had coronary angiography or prophylactic myocardial revascularisation before surgery.

Dobutamine-atropine stress test: The study protocol was approved by the Hospital Ethics Committee and all patients gave informed consent. In each subject, a resting two-dimensional echocardiographic examination including standard apical and parasternal views of the left ventricle was performed and recorded on video tape. A resting 12-lead electrocardiogram was also obtained. Dobutamine was administered intravenously with an infusion pump, starting at 10 µg/kg/min for 3 minutes (stage I). The infusion rate was increased by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min (stage IV), and continued for 6 minutes. If signs and symptoms of ischemia were absent during stage IV, atropine was given to patients who did

not reach their age-corrected target heart rate [(220-age) X 0.85 in men, and (200-age) X 0.85 in women]. Atropine was administered iv in 0.25 mg increments, to a maximum of 1 mg, while the dobutamine infusion was continued. During the test, the 12-lead ECG was monitored continuously and recorded each minute. Blood pressure was measured noninvasively (Accutorr A1, Datascope Corp., Paramus NY, USA) at rest and at each stage of the protocol. The two-dimensional echocardiogram was monitored continuously and recorded on video tape during the last minute of each stage. A quad-screen video display, for side-by-side comparison of resting and stress images, was used during the last 150 examinations (Vingmed CFM 800, Diasonics Sonatron, Zug, Switzerland). The criteria for stopping the test included a decline in systolic blood pressure of more then 40 mmHg from the resting value or a systolic blood pressure of less than 100 mmHg, significant cardiac arrhythmias, severe chest pain, horizontal or downsloping electrocardiographic ST depression of $\geq$0.2 mV measured 80 ms after the J point, ST-segment elevation of $\geq$0.2 mV, and severe or extensive new echocardiographic wall motion abnormalities.

Off-line assessment of echocardiographic images was performed by two investigators who knew the doses of dobutamine and atropine used, but were blinded to clinical information. The left ventricular wall was divided into 16 segments(23) and wall motion in each was subjectively scored on a four point scale: 1= normal; 2= hypokinetic; 3= akinetic and 4= dyskinetic. The test was considered positive when wall motion in any segment deteriorated one grade or more. Agreement between the two investigators was required for a test to be designated as positive. In the event of disagreement, a third investigator resolved the dispute.

For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress. The severity of ischemia was defined as the difference between these two values. The extent of ischemia was defined as the number of segments exhibiting deteriorating wall motion during stress. The "ischemic threshold" was defined as the heart rate at which new echocardiographic wall-motion abnormalities occurred, divided by the maximal age-related heart rate [(220-age) in men, and (200-age) in women].

Analysis of clinical outcomes: Patients were followed throughout their stay in hospital. On the 1st, 3rd and 7th postoperative days serum creatine kinase with MB-fraction was measured and a 12-lead ECG was recorded. These tests were repeated when necessary, at the discretion of the treating physicians. Adverse clinical outcomes included: 1) cardiac death (based on clinical assessment, cardiac

isoenzymes, ECG and autopsy when available), 2) non-fatal myocardial infarction documented by cardiac isoenzymes (creatine kinase >110 U/l with MB >10%) and ECG (new Q waves >0.03 second), 3) unstable angina consisting of typical persisting chest pain at rest with transient ischemic ECG changes requiring prolonged stay or readmission at the IC and intravenous treatment with nitrates and/or percutaneous transluminal angioplasty.

Statistical analysis: Univariate analysis was performed using the chi-square test with Yates' correction or Fisher's exact test for categorical variables, and Student's t test for continuous variables. Stepwise logistic regression models were fitted to identify independent predictors of a cardiac event. All variables from the univariate analysis, regardless of statistical significance, were entered into the multivariable analysis. The risk associated with a given variable was expressed as an odds ratio (OR) with corresponding 95% confidence intervals (CI). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. Receiver-operator characteristics (ROC) curves were used to determine the optimal ischemic threshold for the prediction of cardiac events.

Results

Patient characteristics: The subject's mean age was 67 years (range 22-90 years) and the majority (257/302) were male. A history of previous myocardial infarction was present in 93 (31%), angina pectoris in 60 (20%) and diabetes mellitus (with drug therapy) in 33 (11%) cases.

Detsky scores of 0-15 points were present in 275 patients, 23 patients had 16-30 points and 4 patients had >30 points. Using Eagle's clinical risk factors(13), 100 patients had no clinical risk factors, 179 patients 1 or 2 risk markers and 21 patients had 3 or more risk factors.

Dobutamine-atropine stress echocardiography: Two patients with severe pulmonary disease were excluded from the study because adequate echocardiographic images were not obtained. Atropine was administered in 101 of 300 patients. Patients taking ß-adrenergic blocking agents prior to the test required atropine more frequently (67/101) than those who were not (34/101) (p=0.004). Test end-points were: target heart rate in 276 patients (92%), severe angina in 17 (5.6%) and side effects in 7 (2.3%). The side-effects causing termination of the test were: ventricular fibrillation in one, paroxysmal atrial fibrillation in two, hypotension in one, severe hypertension (240/130 mmHg) in one, and chills in two patients. Cardiac arrhythmias all occurred in the recovery phase of the test, in these patients test results were available. In the four other patients the test was inconclusive, in the perioperative period no events occurred.

Cardiac arrhythmias developed in 15 patients (5%). These included sustained ventricular tachycardia in three; non sustained ventricular tachycardia in eight and paroxysmal atrial fibrillation in three patients. One patient developed ventricular fibrillation during stage IV. This arrhythmia was terminated with a single countershock and the patient suffered no sequelae. Two patients with sustained ventricular tachycardia responded quickly to discontinuation of dobutamine, while another received i.v. metoprolol. Paroxysmal atrial fibrillation reverted to sinus rhythm after discontinuation of dobutamine plus administration of i.v. metoprolol in two patients and i.v. digoxin to one. Mild hypotension (decline in systolic blood pressure of >20 mmHg) occurred in 12 patients (4%), hypertension (systolic blood pressure >220 mmHg) in 3 (1%) and chills in 7 (2%).

New wall motion abnormalities occurred in 72/300 patients, 12 of whom had a normal wall motion at rest. Six patients had a left bundle branch block, making interpretation of ST-segment changes impossible. New ST-elevation or depression >1 mm during testing occurred in 68 patients and angina in 42. In all patients new wall motion abnormalities preceded the occurrence of stress induced angina.

Cardiac events: Twenty-seven patients experienced cardiac events between days 1 and 7. These included fatal myocardial infarction in 5, non-fatal myocardial infarction in 12 and unstable angina in 10.

Predictive value of clinical variables and test:

1) *Clinical variables:* The Detsky score in patients with a cardiac event was significantly higher than in those without events (12.0 ± 8.1 vs 6.5 ± 5.4, $p < 0.01$). Cardiac events occurred in 22/275 "low-risk"patients (0-15 points), 4/23 "intermediate-risk" patients (16-30 points) and 1/4 "high-risk" patients (>30 points).

One cardiac event occurred among 100 patients (1%) with no clinical risk factors (i.e. "low-risk) according to "Eagle's" criteria. The event rate was 20/181 (11%) in "intermediate-risk" patients with one or two risk factors and increased to 6/21 ((29%) in "high-risk" patients with more than two risk factors ($p < 0.001$).

2) *Univariate analysis:* a) Clinical variables: Significant univariate clinical predictors of perioperative events were a history of angina (OR 4.6, 2.0-10), previous myocardial infarction (OR 4.1, 1.8-9.2) and diabetes mellitus (OR 3.2, 1.3-8.4). Other clinical variables including age, gender, history of hypertension, smoking, heart failure, use of anti-anginal medication and type of surgery (abdominal vs infrainguinal) were not predictive of perioperative events. b) Echocardiographic variables: Perioperative cardiac events were more frequent in patients with echocardiographic wall motion abnormali-

ties at rest (OR 3.7, 1.6-8.3). All 27 patients with cardiac events had new wall motion abnormalities during stress. Consequently, patients with a positive test were more likely to have cardiac events (OR 124, 17-934). The positive predictive value of new wall motion abnormalities in this study was 38% (CI 26-50). Ischemic ST-segment changes were less strongly correlated with perioperative events (OR 4.9, 2.2-11) and the occurrence of angina during stress was unrelated to outcome (OR 1.8, 0.6-4.6).

Multivariable analysis of clinical data and stress test results revealed only one independent predictor of cardiac events, new wall motion abnormalities (OR 124, 17-934).

Among patients with new wall motion abnormalities, quantification of the extent and severity of stress induced wall motion abnormalities was not correlated with perioperative cardiac events (Table 1). However, the heart rate threshold at which ischemia occurred provided additional prognostic information. Among patients with cardiac events the ischemic threshold was 67% (CI 63-71) of the age-corrected maximum heart rate, compared to 80% (CI 77-83) in patients without events ($p < 0.01$). Using the ROC-curve analysis, the best "cut-off" point for the heart rate ischemic threshold was estimated to be 70%. There were 20 postoperative cardiac events among 38 patients in whom ischemic wall motion abnormalities developed at a heart rate of £70% of the age-corrected maximum heart rate (positive predictive power = 53%). In contrast there were 7 cardiac events among 34 patients with a heart rate threshold of >70% (positive predictive power = 21%). All patients with cardiac death had ischemia at a low threshold (65%, CI 58-71). The characteristics of patients with a fatal perioperative cardiac event are presented in Table 2.

Discussion

This study demonstrates the utility of dobutamine-atropine stress echocardiography for preoperative cardiac risk stratification in candidates for major vascular surgery. The test was especially effective for defining a low-risk group with a very low incidence of perioperative cardiac complications. There were no cardiac events among 228 patients with a negative test (negative predictive power 100%, CI 98-100%). A positive test greatly increased the likelihood of a perioperative cardiac event (OR 124, CI 17-934) and was the sole independent predictor of cardiac events. There were 27 perioperative cardiac complications among 72 patients with a positive stress test (positive predictive power= 38%, CI 26-50).

Surprisingly, quantifying the extent and severity of stress-induced wall motion abnormalities did not provide additional risk stratifica-

Table 1 - Semiquantitative analysis of dobutamine-atropine stress test in patients with a positive test (new wall motion abnormalities during stress) (n = 72).

		All cardiac events (n=27)	Cardiac death / infarction (n=17)	No events (n=45)	p value
		mean ± CI	mean ± CI	mean ± CI	
1	Threshold	67 (63-71)	62 (57-67)	80 (77-83)	<0.01
2	Extent	3.3 (2.3-4.3)	3.4 (2.2-4.6)	3.6 (2.5-4.7)	NS
3	Severity	1.5 (1.4-1.7)	1.5 (1.3-1.7)	1.6 (1.4-1.8)	NS

Threshold= heart rate increment at which echocardiographic detected myocardial ischemia occurs ((heart rate ischemia-heart rate rest : age-predicted maximal heart rate-heart rate rest)%); extent= number of ischemic segments during stress; severity= difference between wall motion score at peak stress and rest; CI= 95% confidence interval; NS= not significant.

Table 2 - Clinical data and dobutamine stress test results on patients with perioperative cardiac death.

Pt	age (yrs)	AP	MI	days	WMSI-R	NWMA	threshold	extent	severity
1	70	no	yes	3	1.48	yes	68	4	0.24
2	76	no	yes	5	1.96	yes	63	5	0.42
3	76	yes	yes	5	1.24	yes	64	6	0.36
4	62	no	no	3	1.00	yes	62	4	0.24
5	85	no	yes	7	1.54	yes	66	4	0.18

Pt= patient; AP= angina pectoris; MI= history of previous myocardial infarction; WMSI-R= wall motion score index at rest; NWMA= new wall motion abnormalities; threshold= heart rate increment at which echocardiographic detected myocardial ischemia occurs ((heart rate ischemia : age-predicted maximal heart rate)%); extent= number of ischemic segments; severity= difference between wall motion score at peak stress and rest.

tion among patients with a positive test. However, consideration of the heart rate threshold at which ischemia occurred significantly enhanced risk stratification. Patients with cardiac events became ischemic at significantly lower heart rates than those without ((67%, CI 63-71) vs (80%, CI 77-83) of the age-corrected maximum heart rate). An ischemic threshold of 70% of the age-corrected maximum heart rate provided optimum risk stratification. This threshold defined a high-risk group of 38 patients with an ischemic threshold (<70%) in which 20 cardiac events occurred (positive predictive value 53%). This high-risk group included all 5 cardiac deaths and 8 of 12 nonfatal infarctions (76% of "hard" cardiac events). There were only 7 events in an intermediate-risk group of 34 patients with new wall motion abnormalities at a high ischemic threshold (positive predictive value 21%) (Figure I).

Our results regarding the prognostic value of the ischemic "threshold" during dobutamine stress testing are in agreement with those

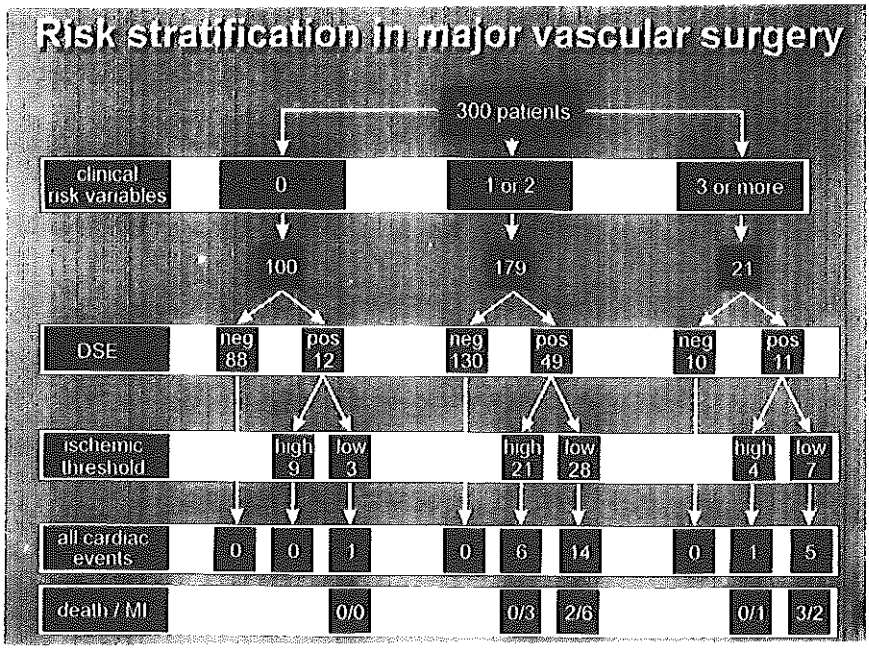

Figure 1 - Breakdown of clinical variables and dobutamine stress test results for perioperative outcomes as applied to this group of 300 patients. Clinical variables are age > 70 years, angina, diabetes requiring treatment, Q waves on electrocardiogram and history of ventricular ectopic activity; DSE = dobutamine-atropine stress test; Events refers to cardiac death, nonfatal myocardial infarction and unstable angina pectoris; Ischemic threshold = the heart rate at whic new echocardiographic wall-motion abnormalites occurred, divided by the maximal age-corrected heart rate, [(220-age) in men, and (200-age) in women]; High-threshold = new echocardiographic wall-motion abnormalities occurred at > 70% of maximal age-corrected heart rate; Low-threshold = new echocardiographic wall-motion abnormalities occurred at ≤ 70% of maximal age-corrected heart rate.

reported by Cutler et al(8) using exercise electrocardiography. They found that cardiac complications occurred most frequently in patients who developed ischemic ST-segment depression at <75% of the predicted maximum age-related heart rate.

We were surprised that quantifying the extent and severity of stress-induced ischemia did not enhance the tive power of dobutamine-atropine stress echocadiography. Other investigators, using dipyridamole-thallium myocardial scintigraphy, have demonstrated that the extent and severity of redistribution defects enhanced the tive value of this test(24). A possible explanation for these different findings is that malperfusion precedes ischemia during dipyridamole infusion and scintigraphy detects both conditions. In contrast, positivity of stress echocardiography is based only on the presence of ischemia.

The dobutamine-atropine stress test caused three serious complications in this study (ventricular fibrillation in one and paroxysmal atrial fibrillation in two). There where no fatal complications. This confirms previous findings about the safety of the stress test(22).

The present study has several unique features compared to previous publications: 1) we studied a large group of consecutive patients; 2) test results were not used for clinical decision making; 3) a comprehensive analysis of stress test results, including the severity, extent and heart rate threshold of ischemia was applied. These features increase our confidence in the reliability of our results. The findings are consistent with previous work, including our own. All earlier studies found that preoperative pharmacologic stress echocardiography has excellent negative tive power for perioperative cardiac events (95-100%) (Table 3). Moreover, most early studies found the positive tive power to be relatively low (21-42%). The exception is the work of Tischler et al(20). In the only study using dipyridamole stress

Authors	Stress	Nr of pts	Se	Sp	+ PV	- PV	Nr of events	Events
Tischler(20)	Dipy	109	88	98	78	99	8	CD, MI, UAP, CHF
Lane(17)	Dobu	38	100	56	21	100	4	CD, MI, UAP
Poldermans(21)	Dobu	131	100	83	42	100	15	CD, MI, UAP, CHF
Lalka(18)	Dobu	60	85	44	29	95	13	CD, MI, UAP
Eichelberger(16)	Dobu	70	100	66	19	100	5	MI,UAP

Dipy= dipyridamole; Dobu= dobutamine; Nr= number; pts= patients; Se= sensitivity%; Sp= specificity%; + PV= positive predictive value%; - PV= negative predictive value%; CD= cardiac death; MI= myocardial infarction; UAP= unstable angina pectoris; CHF= congestive heart failure.

Table 3 - Review of value of new wall motion abnormalities detected by stress echocardiography for preoperative risk stratification of perioperative cardiac events in patients scheduled for major vascular surgery.

echocardiography, these authors found a positive tive power of 78%. There are several possible explanations for this different result. First dipyridamole-induced ischemia might be a less sensitive but more specific indicator of severe coronary artery disease than caused by dobutamine/atropine. Consistent with this hypothesis, the sensitivity of dipyridamole stress echocardiography was 88% in the study of Tischler et al, versus 100% in our study, and two other publications(16,17,21). Alternatively, methodological differences might explain the results. The study by Tischler was relatively small (n=109), and there were few cardiac events (n=8). In addition, differences in the patient population and selection criteria may have been operative. These differences in study design make it impossible to draw definite conclusions about the relative efficacy of dipyridamole or dobutamine as pharmacologic stressors.

Our experience shows that clinical risk assessment using Detsky's scoring system is too insensitive for use as a screening tool in vascular surgery candidates. In our study, 22/27 cardiac events occurred in patients with a relatively low Detsky score of 0-15 points. Detsky system is a modification of Goldman's cardiac risk index, which is itself a specific but relatively insensitive indicator of risk(25). Furthermore, the cardiac risk index was derived from a general surgical population undergoing a variety of surgical procedures rather than the relatively unique vascular surgery population in this study.

In contrast, the clinical risk factors defined by Eagle et al(13) in a study of vascular surgery candidates were useful in our study group. There was only one cardiac event (unstable angina pectoris) among 100 patients with none of Eagle's five clinical tors (angina, diabetes requiring drug therapy, age >70 years, Q wave on ECG and history of ventricular ectopic activity requiring treatment). The negative tive power of no Eagle criteria was 99%, CI 98-100. This is consistent with the negative tive power of 96.9% in Eagle's study, and 96.8% noted by Lette et al(6). This result is not surprising, considering that the three univariable clinical tors of perioperative cardiac risk that we noted (angina, diabetes and previous myocardial infarction) are similar to those noted by Eagle et al.

Based on these results, we do not recommend routine preoperative pharmacologic stress echocardiography in all vascular surgery candidates. Patients with none of Eagle's clinical risk factors appear to represent a low-risk population (33% of our patients), in whom further cardiac evaluation may be unnecessary. We recommend that the remaining patients (with one or more clinical risk factors) undergo stress echocardiography preoperatively. This test identifies another large low-risk population (70% of the remaining patients) with negative test results. Avoiding additional testing and/or expensive

risk-reduction strategies (e.g. coronary angiography and myocardial revascularisation) in these patients has the potential to conserve health-care resources. The test also defines an intermediate risk group with a positive stress test but a high ischemic threshold. The optimum management of these patients is unclear.

Patients with a positive pharmacologic stress test and a low ischemic threshold (heart rate <70% of the age-corrected maximum heart rate) are extremely high-risk, and the advisability of surgery should be carefully reconsidered.

The optimum management of the very high-risk patient who must undergo major vascular surgery because of life or limb-threatening disease is unknown. Various risk-reduction strategies including intensive perioperative monitoring and intervention(2,6,27), perioperative beta-adrenergic blockade with ultra-short acting beta blockers like esmolol(2), stress suppression with regional anaesthesia and analgesia(28), and prophylactic myocardial revascularisation(3,27) have been proposed. However, the efficacy of these techniques has never been adequately investigated and their benefits are unproven.

Dobutamine-atropine stress echocardiography clearly defines a high-risk population of patients in whom the utility of these previously untested risk-reduction strategies can be prospectively assessed. This may represent the most immediate application of the test.

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CHAPTER XII

SUSTAINED PROGNOSTIC VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR LATE CARDIAC EVENTS AFTER MAJOR NONCARDIAC VASCULAR SURGERY*

Abstract

Background: Late cardiac events after major noncardiac vascular surgery are an important cause of morbidity and mortality. We studied the prognostic value of perioperative dobutamine stress echocardiography, relative to clinical risk assessment, for predicting late cardiac events.

Methods: Three hundred and sixteen patients undergoing major vascular surgery were studied. All patients underwent clinical evaluation for the presence of cardiac risk factors (smoking, hypertension, angina, diabetes, history of heart failure, previous infarction and age >70 years) and dobutamine stress echocardiography. Left ventricular wall motion was evaluated at rest and the extent and severity of stress-induced new wall motion abnormalities occurred was noted. Patients were followed perioperatively and for 19 $\pm$ 11 months postoperatively and the occurrence of cardiac events was noted. Uni- and multivariate Cox proportional-hazard regression models were used to identify predictors of late cardiac events.

Results: Thirty-two cardiac events occurred (11 cardiac deaths, 11 nonfatal myocardial infarctions and 10 patients with unstable angina). By multivariate regression analysis the occurrence of extensive ($\geq$ 3 segments) or limited (1-2 segments) stress-induced new wall abnormalities and previous infarction independently predict late cardiac events, elevating the risk by 6.5, 2.9 and 3.8 fold respectively. The severity of ischemia during stress and heart rate threshold for ischemia were not independently predictive.

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Conclusion: Patients with a history of myocardial infarction or stress-induced ischemia have a high risk of fatal and non-fatal cardiac events after vascular surgery. Patients with both a history of infarction and extensive stress-induced ischemia are especially high-risk, and deserve intensive management.

Introduction

Coronary artery disease is a major cause of late morbidity and mortality in survivors of major vascular surgery. For example, Krupski et al (1) found that cardiac occurred in 19% of 129 patients followed for two years after vascular surgery. The high incidence reflects the frequency and severity of underlying coronary artery disease. Hetzer et al (2) obtained coronary angiograms in 1000 vascular surgery candidates and found severe correctable coronary artery disease in 36% of patients with aortic aneurysm and in 28% of those with lower extremity ischemia. Therefore, the preoperative evaluation of vascular surgery candidates should include an assessment of the risk of late postoperative cardiac events, since these will determine the likelihood that individual patients will survive to enjoy the benefits of successful surgery.

Several clinical and laboratory variables have been associated with an increased risk of late cardiac events after major surgery. Clinical predictors include a preoperative history of coronary artery disease or congestive heart failure (2,3). Of particular interest is the finding by Mangano et al (4) that patients who survived a postoperative myocardial infarction or episode of unstable angina had a 20-fold increase in the odds of a late cardiac event. Non-invasive laboratory indicators of late cardiac risk include left ventricular dilatation and thallium redistribution during dipyridamole-thallium myocardial perfusion scintigraphy (4-8), impaired left ventricular function on radionuclide ventriculography (9) and ischemic ST-segment changes on perioperative ambulatory electrocardiographic monitoring (10,11).

We have found dobutamine stress echocardiography to be an extremely useful tool for the assessment of perioperative cardiac risk in patients undergoing major vascular surgery (12,13). Therefore, we hypothesized that this would also predict the risk of late cardiac events after major vascular surgery. Dobutamine and atropine unfavourably alter myocardial oxygen balance and may induce ischemia in patients with coronary artery disease (14,15). Pharmacologically-induced ischemia can be detected echocardiographically as new regional wall motion abnormalities. The test is safe, inexpensive, widely available and applicable in patients who cannot exercise. It also provides information about resting left ventricular function. This report summarizes

data from 316 patients who were followed for up to 36 months after major vascular surgery.

Methods

Patient characteristics: The study protocol was approved by the Hospital Ethics Committee and all patients gave informed consent. Between 1991 and 1994 we studied 318 consecutive patients. Beta blockers were used by 72 (23%) patients and calcium antagonists by 89 (28%). Five patients suffered fatal perioperative myocardial infarction, and 2 more were lost to follow-up. The remaining 316 survivors form the basis of this report. These included 264 men and 52 women, aged 22 to 90 years (mean 67). They underwent aortic aneurysm resection (n= 111), aortofemoral bypass (n=111) or infrainguinal arterial reconstruction (n=94). Preoperative clinical examination included a history, physical and twelve-lead electrocardiogram (ECG). We specially searched for clinical cardiac risk factors. These included: smoking, hypertension, angina, diabetes mellitus, history of congestive heart failure, age >70 years and previous myocardial infarction (Q wave on ECG). The occurrence of a non fatal perioperative cardiac event (i.e. unstable angina or myocardial infarction) were also noted.

Dobutamine stress echocardiography: Preoperatively, each subject underwent dobutamine stress echocardiography. A resting two-dimensional transthoracic echocardiographic examination, including standard apical and parasternal views of the left ventricle, was performed and recorded on video tape. A resting 12-lead ECG was also obtained. Dobutamine was administered intravenously with an infusion pump, starting at 10 µg/kg/min for 3 minutes (stage I). The infusion rate was increased by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min (stage IV), and continued for 6 minutes. If signs and symptoms of ischemia were absent during stage IV, and the patient did not reach a target heart rate [(220-age) X 0.85 in men, and (200-age) X 0.85 in women], atropine was administered iv in 0.25 mg increments, to a maximum of 1 mg, while the dobutamine infusion was continued. During the test, the 12-lead ECG was monitored continuously and recorded each minute. Blood pressure was measured noninvasively (Accutorr A1, Datascope Corp., Paramus NY, USA) at rest and at each stage of the protocol. The two-dimensional echocardiogram was monitored continuously and recorded on video tape during the last minute of each stage. A quad-screen video display, for side-by-side comparison of resting and stress images, was used during the last 150 examinations (Vingmed CFM 800, Diasonics Sonatron, Zug, Swit-

zerland). The criteria for stopping the test included a decline in systolic blood pressure of more then 40 mmHg from the resting value or a systolic blood pressure of less than 100 mmHg, significant cardiac arrhythmia's, severe chest pain, horizontal or downsloping electrocardiographic ST depression of ³0.2 mV measured 80 ms after the J point, ST-segment elevation of 0.2 mV in the absence of Q waves, and severe new echocardiographic wall motion abnormalities in multiple location.

Off-line assessment of echocardiographic images was performed by two investigators who knew the doses of dobutamine and atropine used, but were blinded to clinical information. The left ventricular wall was divided into 16 segments (16) and wall motion was subjectively scored on a four-point scale: 1= normal; 2= hypokinetic; 3= akinetic and 4= dyskinetic. The test was considered positive when wall motion in any segment deteriorated one or more grades. Agreement between the two investigators was required for a test to be designated as positive. In the event of disagreement, a third investigator resolved the dispute.

For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress. The *severity* of ischemia was defined as the difference between these two values. The *extent* of ischemia was defined as the number of segments exhibiting deteriorating wall motion during stress. The *ischemic threshold* was defined as the heart rate at which new echocardiographic wall-motion abnormalities occurred, divided by the maximal age-related heart rate (220-age in men, and 200-age in women).

Follow-up: All patients left hospital within one month of surgery. Thereafter, they visited our hospital out-patients clinic at regular intervals for 19±11 months (mean ± SD) (range 1-36 months) . If a patients did not appear for a scheduled visit, his family physician was contacted. The physician performing the follow-up was blinded to the results of preoperative dobutamine-atropine stress echocardiography, because the test was still considered investigational at that time. Therefore, postoperative management was not influenced by preoperative stress testing. The occurrence of all late cardiac events (cardiac death, nonfatal myocardial infarction and myocardial revascularization) was documented. "Hard" cardiac events were defined as nonfatal myocardial infarction or cardiac death. The occurrence of stroke and noncardiac death were also noted. Cardiac death was determined by reviewing the clinical presentation, including cardiac isoenzymes, 12-lead ECG, and autopsy results when these were available. Nonfatal myocardial infarction was defined as elevated cardiac isoenzymes (creatinine kinase >110 U/L with MB-isoenzymes

>10%) and ECG changes (new Q waves >0.03 second). Myocardial revascularisation included coronary artery bypass grafting or percutaneous transluminal angioplasty. When more than one cardiac event occurred in the same patient, the most serious event was considered for analysis (i.e. death > myocardial infarction > revascularisation).

Statistical analysis: Uni- and multivariate Cox proportional-ha ards regression models were used to identify independent predictors of late cardiac events. The risk associated with a given variable was expressed by hazard ratio (HR) with corresponding 95% confidence interval (CI). Variables were considered to be significant if the null hypothesis of no contribution could be rejected at the 0.05 probability level. In addiction, likelihood ratios were computed to describe the predictive utility of significant risk factors. Kaplan-Meier life-table analysis of cardiac events was used to assess the prognostic importance of stress-induced new wall motion abnormalities with respect to event-free survival.

Receiver-operator characteristics (ROC) curves were used to determine the "optimal" cut-off point for prediction of late events with respect to: 1) the number of segments with resting wall motion abnormalities, 2) the number ischemic segments at peak stress, 3) the ischemic heart rate threshold, and 4) the severity of ischemia at peak stress. The best cut-off was defined as the point with the highest sum of sensitivity and specificity.

Results

Clinical profile and resting echocardiogram: One hundred seventy two patients (54%) were over 70 years of age, smoking was present in 104 (43%), hypertension in 64 (20%), typical angina in 57 (18%), previous myocardial infarction in 92 (29%), a history of heart failure in 13 (4%), and diabetes mellitus in 32 (10%). Twenty-two (7%) patients experienced a nonfatal perioperative cardiac event.

Resting wall motion abnormalities were present in 102 (32%). In 48 (15%) patients more than 3 segments were abnormal at rest.

Hemodynamic data: Heart rate increased from 73 $\pm$14 bpm to 132$\pm$15 bpm (p=0.0001) Systolic blood pressure increased during dobutamine infusion from 144$\pm$25 mmHg to 153$\pm$32 mmHg (p=0.001). Diastolic blood pressure decrease from 83$\pm$14 mmHg to 80$\pm$17 at the maximum dose of dobutamine (p=0.01).

Stress test results: During the stress test 25(8%) patients experienced typical chest pain, 74(23%) ST-segment changes, and 84(25%) new wall motion abnormalities. The mean dobutamine dose

was 36 μg/Kg/min, and atropine was administrated to 111 (35%) patients. The stress test was inconclusive (prematurely stopped due to side-effects without signs or symptoms of myocardial ischemia) in 4 patients. Two of these patients developed intolerable chills, one marked hypertension (240/130 mmHg), and one severe hypotension.

Side effects: There were no fatal complications. Besides chest pain, hypotension and cardiac arrhythmias were the most important side effects of dobutamine stress test. Cardiac arrhythmias occurred in 7(2%) patients and hypotension in 12(4%). Cardiac arrhythmias consisted of ventricular fibrillation in 1 patient, nonsustained ventricular tachycardia in 3, paroxysmal atrial fibrillation in 3. The patients who developed ventricular fibrillation, during the recovery phase of the test, was successfully resuscitated with one counter shock. No electrocardiographic or enzymatic evidence of a new myocardial infarction was subsequently apparent. Hypotension was usually mild (decline of systolic blood pressure of >20 mmHg compared to baseline). Stress test results were available in all these patients as cardiac arrhythmias occurred during the recovery phase of the test and patients with mild hypotension were able to continue the test.

Follow-up: Thirty-two cardiac events occurred during follow-up in 316 patients (10.1%). There were 11 cardiac deaths, 11 nonfatal infarctions and coronary revascularisation was performed in 10 patients. Eight patients had a stroke and there were 7 noncardiac deaths (mostly secondary to infected prosthetic grafts). Among 22 patients who experienced a nonfatal perioperative cardiac event, 11 late cardiac events occurred during follow-up. Two of these 11 events were fatal. There were no late cardiac events in the four patients in whom the stress test was prematurely discontinued due to side effects.

Prediction of late cardiac events: ROC-curve analysis defined the following optimal cut-off point for predicting of late events: 1) Resting wall motion abnormalities, ≥ 2 segments, 2) Extent of ischemia, ≥ 3 segments, 3) Heart rate threshold, echocardiographically-detected new wall motion abnormalities at a heart rate of $\leq 70\%$ of the maximal age and sex related value, and 4) Severity of ischemia, (wall motion score at peak stress-wall motion score at rest divided by the number of segments) > 0.14 wall motion score units.

The univariate predictors of late cardiac events (all cardiac events and "hard" cardiac events) are presented in tables I and II. A history of angina, myocardial infarction, or the occurrence of a nonfatal perioperative cardiac event were significant predictors of both all and "hard" late cardiac events. Diabetes mellitus and a history of heart failure were significant predictors of all cardiac events only. Stress test results were also predictive. Left ventricular dysfunction at rest (≥ 2 segments), extensive new wall motion abnormalities during stress

Table I and II - Univariate predictors of all cardiac events (cardiac death, myocardial infarction or coronary revascularization) and "hard cardiac events" (cardiac death or myocardial infarction), after major vascular surgery (n = 316, follow-up period 19 ± 11 months).

Characteristic	All cardiac events, hazard ratios (95% CI)	Hard cardiac events, hazard ratios (95% CI)
Perioperative cardiac events	4.7 (2.5-9.6)	3.4 (1.6-7.4)
Previous myocardial infarction	4.5 (2.2-9.0)	3.4 (1.5-7.4)
History of heart failure	3.4 (1.2-9.9)	NS
Angina pectoris	3.1 (1.5-6.0)	2.9 (1.2-7.4)
Diabetes mellitus	2.6 (1.2-5.7)	NS

Characteristic	All cardiac events, hazard ratios (95% CI)	Hard cardiac events, hazard ratios (95% CI)
Ischemia ≥3 segments	9.0 (4.5-18.2)	8.8 (3.7-20)
NWMA	7.9 (3.7-17)	5.6 (2.5-12)
Low ischemic heart rate threshold	5.6 (2.5-12)	4.5 (1.6-12)
Severity of ischemia	3.1 (1.4-6.8)	NS
ST changes during stress	3.0 (1.5-6.0)	3.9 (1.8-9.0)
Angina during stress	2.9 (1.2-7.4)	NS
Resting wall motion abnormalities ≥2 segments	2.7 (1.3-5.5)	2.4 (1.1-5.5)

NWMA = any new wall motion abnormalities; Low ischemic threshold: echocardiographic detected ischemia at a heart rate of <70% of the maximal age and sex related heart rate; Severity of ischemia: difference between wall motion score at peak stress - wall motion score at rest >0.14.

Table III - Multivariate predictors of all cardiac events (cardiac death, myocardial infarction or coronary revascularization) and "hard cardiac events" (cardiac death or myocardial infarction) after major vascular surgery (n = 316, follow-up period 19 ± 11 months).

	All cardiac events, hazard ratios (95% CI)	Hard cardiac events, hazard ratios (95% CI)
Ischemia during stress ≥3 segments	6.5 (3.0-15)	5.8 (2.5-15)
Ischemia during stress 1-2 segments	2.9 (1.1-7.8)	NS
Previous myocardial infarction	3.8 (1.6-8.2)	2.8 (1.1-6.7)

CI = confidence interval, NS = not significant.

Table IV - Hazard ratios for all late cardiac events as a function of the presence of a previous myocardial infarction and the extent of stress-induced ischemia.

Ischemic segments during DSE	Previous myocardial infarction	No. patients	Event rate	Hazard ratios (95% CI)
0	no	183	7/183(4%)	1.0 (1.0-1.0)
0	yes	49	4/49(8%)	3.1 (1.4-6.6)
1-2	no	15	1/15(7%)	2.9 (1.1-7.8)
1-2	yes	22	6/22(27%)	8.8 (3.1-25.2)
≥3	no	26	3/26(12%)	10.3 (4.5-23.4)
≥3	yes	21	11/21(52%)	31.5 (11.4-87.3)

DSE = dobutamine stress test.

(≥ 3 segments), any new wall motion abnormalities during stress, the heart rate threshold for ischemia (>70% of the maximal age and sex related heart rate), the severity of stress-induced ischemia and stress-induced angina or ST-segment changes also predicted all late cardiac events. With the exception of ST-segment changes and severity of ischemia during the stress these test variables were also predictive for "hard" cardiac events. Stroke could not be predicted by clinical risk factors or stress test results.

Multivariate regression analysis was performed on all clinical risk factors and stress test results (table III).

Extensive echocardiographically-detected ischemia during stress was the most powerful predictor of all as well as "hard" late cardiac events. A previous myocardial infarction was also an independent predictor of fatal and nonfatal late cardiac events after surgery. Event-free survival curves for patients with a normal stress test limited ischemia (1-2 segments), and extensive ischemia (≥ 3 segments) during the stress are presented in fig 1. There was a significant decrease in event-free survival in patients with either limited or extensive new wall motion abnormalities.

The hazard ratios for the occurrence of late cardiac events are presented in Table IV and fig 2. Patients with no history of myocardial infarction and a negative test were no risk for late cardiac events (HR, 1.0). Patients with either limited ischemia or a history of infarction were relatively low risk (HR, 2.9 and 3.1 respectively). Patients with limited ischemia and history of infarction, or extensive ischemia without previous infarction were moderately highly risk (HR, 8.8 and 10.3 respectively). Those with both extensive ischemia and history of infarction were extremely high risk (HR, 31.5).

Discussion

Patients undergoing major vascular surgery represent a high-risk population, with respect to the risk of both perioperative and late cardiac events (1,16,18).

The decision to proceed with the surgery should include a consideration of both these risks. Ideally, a patients should not only survive the perioperative period intact, but also live long enough to enjoy the benefits of successful surgery (17).

Non-invasive preoperative risk stratification in patient scheduled for major vascular surgery may help in appropriate decision-making.

Pharmacological stress echocardiography is a promising tool in this context, since it is widely available, generally applicable and less expensive than perfusion scientigraphy (12-16). This study demonstrates that dobutamine stress echocardiography is the most

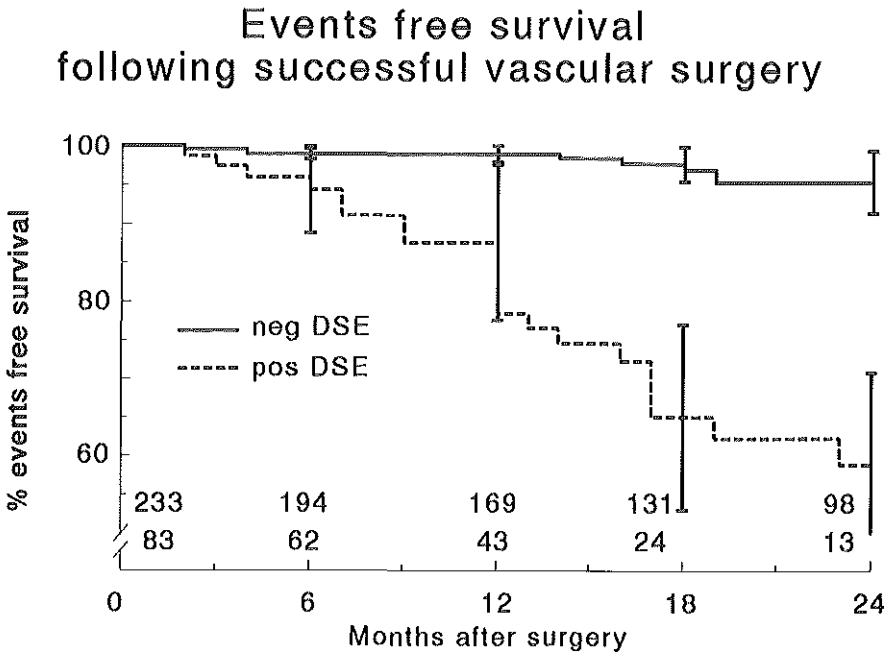

Figure 1 - Kaplan-Meier curves for cardiac events (cardiac death, myocardial infarction or coronary revascularizarion) during follow-up as a function of the extent of ischemia (0.1-2, or > 3 segments) during dobutamine-atropine stress testing. Each plot represents the cumulative percentage of patients remaining events free. Vertical lines representing 95% confidence interval.

powerful predictor of late cardiac events after major vascular surgery, and is superior to simple clinical risk assessment. The negative prognostic value of extensive stress-induced ischemia (≥ 3 segments) applies to both all and "hard" cardiac events increasing risk by 6.5 and 5.8 times respectively. Limited stress-induced ischemia increased the risk of "all" late events 2.9 times. The only independent preoperative clinical risk factor was a history of myocardial infarction. The presence of this risk factor increase the risk of "all" and "hard" late events by 3.8 and 2.8 times respectively.

A combination of semi-quantitative stress echocardiography and the clinical history allows us to define the risk of all late cardiac events for patients in six different categories (Tables IV and figure 2). the absence of previous myocardial infarction, combined with a negative stress test defines a large subset of patients (183/316, 58%) with a very low rate of late events (HR, 1.0). Patients with either limited ischemia or a previous myocardial infarction were also relatively low-risk (HR, 2.9-3.1). Patients with both limited ischemia and a history

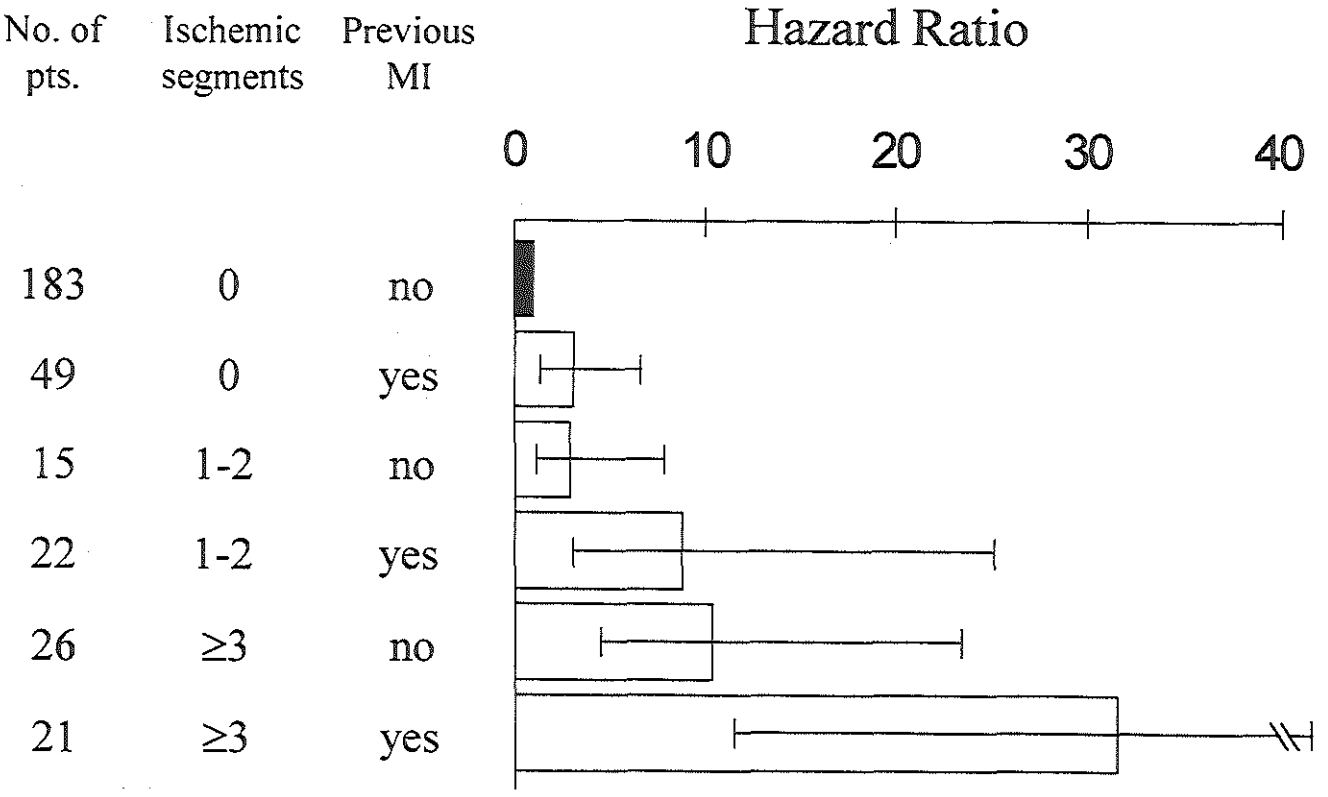

Figure 2 - Hazard ratios for all late cardiac events after major vascular surgery (i.e. cardiac death, myocardial infarction or coronary revascularizarion) as a function of the extent of new wall motion abnormalities during dobutamine stress echocardiography, and the presence or absence of preoperative myocardial infarction. Error bars represent 95% confidence intervals.

of myocardial infarction were relatively high risk (HR, 8.8), as were those with extensive ischemia without previous infarction (HR, 31.5).

This approach defines a relatively large subset of low and relatively low risk patients

(247/316, 78%) who need not undergo intensive postoperative follow-up. In patients with a relatively high risk of late cardiac events, meticulous follow-up is clearly indicated. In a very high-risk patients with extensive stress-induced ischemia and history of myocardial infarction, an aggressive "anti-ischemic" approach might prolong the period of event-free survival after successful surgery. However, this hypothesis remains untested, and the optimal "anti-ischemic" approach remains undefined.

We have previously recommended preoperative dobutamine stress echocardiography for the assessment of *perioperative* cardiac risk in all patients with inadequate physical exercise capacity, or any of the clinical risk factors defined by Eagle et al (i.e. age >70 years, Q-wave on ECG, angina pectoris, diabetes mellitus or a history of ventricular tachyarrhythmias) (12,19). This same recommendation also appears appropriate for preoperative assessment of the risk of *late* cardiac events. In our study, only six patients with an adequate physical exercise capacity and no Eagle criteria had a positive stress test. None of these six patients suffered a late cardiac event. We recommend that dobutamine stress echocardiography be performed preoperatively in all patients with one or more of Eagles risk factors or an inadequate physical exercise capacity to define the risk of late cardiac events after surgery.

Previous study in non-surgical patients have demonstrate a relationship between stress-induced wall motion abnormalities and the risk of subsequent cardiac events in patients with known or suspected coronary disease (15,20).

However, patients presenting for major vascular surgery comprise a very different population in whom the applicability of previous results was undefined. Our study generally confirms previous work in medical patients, but provides unique insight into the role of pharmacologic stress echocardiography for the assessment of late cardiac risk in patients presenting for major vascular surgery. The semiquantitative analysis of stress test results, combined with a single clinical risk factor provides precise definition of late risk. By studying consecutive patients who underwent surgery we avoided a referral bias. By blinding the attending physicians to test results, we avoided alteration in management based on presumptions about risk.

For example, coronary arteriography and subsequent prophylactic myocardial revascularization were largely avoided. These design fea-

tures, and the relatively sample size, increases the reliability of our conclusions.

Multivariate analysis indicated that the extent of ischemia was an independent predictor of late cardiac events. However, neither the severity of ischemia or the heart rate at which ischemia occurred provided additional prognostic information. These results are in partial agreement with a previous study of Lette at al (17), using quantitative dypiridamole-thallium scintigraphy. That study found that both the extent and the severity of reversible perfusion defects were significant predictors of late cardiac events. The difference between studies regarding the predictive power of the severity of ischemia is unexplained, but methodological differences are presumably involved.

In agreement with the study of Mangano et al (4) and Yeager et al (18) we found that patients who survived surgery but suffered a postoperative myocardial infarction or episode of unstable angina had nearly a 7-fold increase in the risk of a late cardiac event. In Mangano's study, the negative prognostic value of a postoperative ischemic cardiac event was independent of the results of perioperative Holter monitoring. However, in our study the occurrence of a perioperative non fatal infarction or unstable angina was not an independent predictor of adverse late outcome, when multivariate analysis included the results of preoperative stress echocardiography. These different results suggest that the prognostic power of stress echocardiography may be superior to that of perioperative Holter monitoring.

Conclusion

Preoperative dobutamine stress echocardiography is an important new technique for defining the risk of late cardiac events in patients undergoing major vascular surgery.

The test should be performed preoperatively in all patients with an inadequate exercise capacity or any of the clinical risk factors defined by Eagle et al.

Extensive stress-induced ischemia is the most powerful predictor of late cardiac events but a history of myocardial infarction also have independent negative prognostic value.

These conclusion remain valid when only "hard" ischemic events such as cardiac death and myocardial infarction are considered. Preoperative semi-quantitative stress echocardiography combined with information about previous myocardial infarction optimizes assessment of late risk. Patients presenting for vascular surgery with a history of myocardial infarction and extensive stress-induced ischemia are extremely high-risk. This information should be carefully considered

when deciding upon the advisability of surgery, appropriate anti-ischemic therapy, and the need for intensive follow-up.

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CONCLUSIONS

Stress echocardiography is increasingly used for both the diagnosis and risk stratification of patients with suspected or known coronary artery disease.

The first clinical of exercise echocardiography were published in 1979 by the Indianapolis group (1). These investigators concluded that exercises stress echocardiography was feasible and reliable but technically demanding and difficult.

Technological advances provided better image quality and, consequently, higher diagnostic accuracy. More particularly, the development of digital acquisition systems (cine loop) allowed a single cardiac cycle to be sampled and the side by side display of resting and stress data offering advantages for analysis. Pharmacological stress was introduced as an alternative to exercise stress and allowed to record better quality images. These advantages resulted in rapid acceptance of this technique.

Dobutamine stress echocardiography is now increasingly used for the diagnosis of coronary artery disease (2-5), assessment of revascularization procedures and risk stratification in patients after myocardial infarction and prior to major vascular surgery (6-12). Currently, the assessment of viable myocardium in patients with advanced left ventricular dysfunction is an active area of research and the use of "low" dose dobutamine stress echocardiography for it detection is promising.

The studies presented in this thesis sought to study specific aspects of the stress echocardiography for the detection of myocardial ischemia and the demonstration of myocardium viability. Also, the prognostic value in patients prior to major non-cardiac vascular surgery.

Detection of myocardial ischemia

Exercise echocardiography: Exercise stress was the first form of stress used in combination with echocardiography.

Digital technology has allowed better acquisition, display, analysis, storage and retrieval of echocardiographic results, overcoming many of the disadvantages related to exercise echocardiography in particular artefacts caused hyperventilation and chest wall movements.

We studied the relationship between exercise echocardiography and the percent diameter stenosis and minimal lumen diameter

obtained from quantitative coronary arteriography (QCA) in 34 patients without previous myocardial infarction and with a proximal single-site 1-vessel coronary obstruction. The severity of the coronary stenosis predicts an ischemic response during exercise testing. New wall motion abnormalities are better predicted than ST-segment changes on the ECG or angina. The best cut-off point for the prediction of wall motion abnormalities was a minimal coronary luminal diameter of 1.13 mm (sensitivity and specificity 83%).

Using the same approach we selected a sub-group of 31 patients without previous myocardial infarction with a proximal single site 1-vessel disease of the left anterior discending coronary artery. Exercise stress induced new wall motion abnormalities on the echocardiogram and transient perfusion defects by MIBI SPECT were considered as markers of ischemia.

The degree of coronary artery stenosis correlates better with echocardiographic than with scintigraphic markers of exercise induced myocardial ischemia. In fact we found angiographic cut-off values to predict a positive exercise echocardiography and scintigraphic test were similar (diameter stenosis of 52% and minimal lumen diameter of 1.12 mm for echocardiography, 49% and 1.2 mm for SPECT, respectively). However both the sensitivity and specificity at the cross point was slightly higher, but not statistically significant for echocardiography than for SPECT, (diameter stenosis 81% vs. 67% and minimal lumen diameter 81% vs. 74%. It should noted that in our study only patients with single-site 1-vessel left artery descending disease were included.. The few previous comparative studies between exercise echocardiography and perfusion scintigraphy were confounded by the inclusion of patients with previous myocardial infarction or multivessel disease (13-18).

Dobutamine-atropine stress echocardiography: For many years exercise stress testing in combination with nuclear imaging has been used for the non-invasive detection and functional assessment of coronary artery disease. However a substantial number of patients are unable to perform adequate levels of exercise to provoke myocardial ischemia.

Dobutamine stress by increasing oxygen demand of the myocardium is now increasingly used in combination with echocardiography for the evaluation of patients with suspected or known coronary artery disease. Atropine is added at the end of the test when target heart rate is not reached with the maximal dobutamine dose alone. We tested quantitative angiographic parameters to determine the most appropriate cut-off value of each parameter for the onset of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography. Because wall motion abnormalities

are an early and specific indicator of myocardial ischemia, dobutamine-atropine stress echocardiography is potentially superior to stress scintigraphy, particularly in patients with mild to moderate stenoses in whom transient perfusion defects may result from a maldistibution of coronary flow and do not necessarily reflect true myocardial ischemia. Several studies indicate good agreement between the development of wall motion abnormalities during stress echocardiography and the severity of coronary stenosis (11, 15,19-26) . However, those studies had limitations because either visual interpretation of angiograms was performed or arbitrary cut-off points for quantitative angiographic data were used. Therefore, such analytic approaches are not appropriate for the evaluation of new stress modalities. We found that a minimal lumen diameter of 1.07 mm has the best predictive value of a positive dobutamine-atropine echocardiographic stress test. It appears that the minimal luminal diameter is a good parameter to define the physiological importance of coronary stenoses in medium to large sized arteries.

We also studied the significance of akinetic segments which become dyskinetic during a dobutamine-atropine stress echocardiography without improving at low dose suggesting that it could be residual ischemia. However, comparing these segments with the findings of SPECT we concluded that it is a mechanical phenomenon compatible with scar tissue.

Patients with left bundle branch block on their ECG often demonstrate a false positive perfusion defect in the territory of left anterior descending coronary artery (27-29).

The cause of false positive perfusion imaging in these patients remains uncertain. A likely explanation is that the asynchronous activation of the septum may cause it to contract early in diastole, when coronary perfusion is maximal. A perfusion defect may therefore be present at rest or induced by exercise, when diastole is further shortened. The use of vasodilator agent such as dipyridamole, may avoid this problem (28). Other authors have suggested that patients with known left bundle branch block should be diagnosed as having ischemia only when the apex is involved in the perfusion defect.

Echocardiography allows to examine left ventricular wall thickening as well as other left anterior descending territory regions. Previous reports involving a few patients with left bundle branch block have also indicated that stress echocardiography is more specific than perfusion imaging (6)

Our study confirms the higher diagnostic accuracy of dobutamine-atropine stress echocardiography in patients with left bundle branch block. We compare the accuracy of wall thickening abnormalities during dobutamine-atropine stress echocardiography with that of fixed

or reversible defects under perfusion tomography for the non-invasive identification of coronary artery disease in 24 patients with complete left bundle branch block. In the left anterior descending coronary artery territory, sensitivity of dobutamine stress echocardiography and scintigraphy were comparable (83% vs. 100%) while specificity was significantly superior with dobutamine stress echocardiography (92% vs. 9%). This low specificity of perfusion scintigraphy was improved by requiring an associated apical defect to indicate left anterior descending coronary artery disease and by restricting the diagnosis of coronary disease to those patients with partially reversible defects only.

Detection of myocardial viability

The term "viability" includes two different clinical situations: stunned myocardium which refers to regions with prolonged postischemic dysfunction, present despite restoration of normal blood flow and hibernating myocardium which refers to regions of chronic ventricular dysfunction which results from prolonged reduction in blood flow. In these regions myocardial function is restored by myocardial revascularization. Both situations may be present in the same patient. Obviously, the identification of viable myocardium is important for the clinical management of these patients because ventricular function can improve after revascularization. In contrast with myocardial stunning, there is no valid experimental model for chronic hibernation because the pathophysiology of chronic regional dysfunction involving both post-ischemic dysfunction and ongoing reduction of coronary flow is more complex and more difficult to reproduce under laboratory conditions. Recent observations suggest that it could arise from repeated episodes of myocardial stunning, eventually resulting in prolonged post-ischemic dysfunction (30).

Several experimental models confirm that dysfuctioning but viable myocardium may show functional improvement by stimulation with sympathomimetic agents such as isoproterenol, dopamine and dobutamine. The mechanism of this response is unclear, but appears to be an inotropic effect and unrelated to alteration in loading conditions (31-35).

"Low-dose" dobutamine in conjunction with echocardiography has been proposed for the assessment of myocardial viability in akinetic and hypokinetic regions. These segments are considered viable when wall thickening improves during the infusion of dobutamine up to a dose of 10 µg/Kg/min when its inotropic effect is maximal.

Others methods for detecting viable myocardium include positron emission tomography (PET) (36) which is considered the reference method, and scintigraphy with 201Tl reinjection (37-38).

While several studies have addressed the role of low dose dobutamine for the assessment of left ventricular functional recovery in patients with recent myocardial infarction (10,39-42) little data is available on its predictive value for post-revascularization functional improvement. We compared the value of 201Tl scintigraphy and low dose dobutamine echocardiography as methods of assessing myocardial viability. In 38 patients with severe chronic left ventricular dysfunction improvement in systolic thickening after infusion of low dose dobutamine predicted the recovery of function after revascularization. Compared with low dose dobutamine 201Tl scintigraphy has a comparable sensitivity (74% vs. 89%) but a lower specificity (95% vs. 48%). Low dose dobutamine allows to predict the post-operative functional recovery of non-contracting but viable myocardium and our findings are in agreement with others studies (43-44).

Prognostic value

Preoperative cardiac risk stratification: Cardiac risk stratification for patients scheduled for major noncardiac vascular surgery is an important clinical application of dobutamine stress echocardiography (12,45-47).

Perioperative cardiac complications are common and the leading cause of perioperative morbidity and mortality; they also determine long-term survival (48-50). The incidence of perioperative events ranges from 1 to 15%, with a mortality range from 5-10% (48). Several methods have been used to select high cardiac risk patients before surgery (51-54). Since many of these patients are not able to perform adequate physical exercise (because of age, peripheral vascular disease, pulmonary disease or stroke), nonexercise dependent stress tests are important. Until now the most widely used method was a combination of a clinical scoring classification and dypiridamole thallium scintigraphy (54).

In our experience, clinical risk assessment and dobutamine atropine stress echocardiography were performed in 300 patients to evaluate the predictive value of the stress test

The heart-rate at which ischemia occurred defined a high-risk group with a low ischemic threshold and an intermediate-risk group with a high ischemic threshold. Patients who develop ischemia at a low heart rate increment are at highest risk for perioperative cardiac events (positive predictive value of 53% for all fatal complications).

Patients in whom ischemia occurred at a high heart rate are at lower risk of perioperative cardiac events (21%). Patients with no stress induced ischemia had an uneventful perioperative clinical outcome.

Therefore, this method is safe and can be easily used to define a high-risk population of patients in whom risk-reduction strategies can be prospectively planned.

Prognostic value for late cardiac events. Exercise (55), dipyridamole (56) and recently dobutamine (57,58) stress echocardiography have been used as a prognostic test to predict late cardiac events. Several studies reported (47,59-60) a significant relation between new wall motion abnormalities and late cardiac events . We attempted to predict late cardiac death, myocardial infarction, unstable angina pectoris and all cardiac events in patients with suspected coronary disease (58). Using multivariate analysis there was a significant correlation between cardiac death and diffuse wall motion abnormalities at rest (odds ratio 3.9, 1.1-14.2), a history of a previous infarction and a new infarction (odds ratio 16.3, 2.1-128), unstable angina pectoris and new wall motion abnormalities (odds ratio 2.3, 1.3-4.1). If all cardiac events were combined, only new wall motion abnormalities were predictive for late events (odds ratio 2.3, 1.4-3.7).

We also studied the incremental prognostic value of pre-operative dobutamine atropine stress echocardiography to clinical risk factors for late cardiac events after successful major non-cardiac vascular surgery (61).

It was found that new wall motion abnormalities during stress provided additional information to clinical data, particularly in patients with intermediate "clinical" risk.

General limitations

The major limitation of stress echocardiography remains the semi-quantitative subjective analysis interpretation (62)

For exercise stress echocardiography the interobserver variability has been examined in small groups of patients and confined to readers from the same institution (63). Sawada et al. (22) reported agreement between two observer from the same institution on the presence or absence of dobutamine stress echocardiography induced abnormality in 91% of patients. In collaboration with four other experienced centres we studied the interistitutional agreement in the interpretation of dobutamine stress echocardiograms in patients with coronary artery disease without previous infarction. A total of 150 dobutamine stress echocardiograms were interpreted by each centre unaware of any other clinical data. The results of our study showed that the

agreement between different centres was moderate (73%) due to a variety of reasons including interpretation criteria, image storage on video tape and image quality (64).

However for those patients having no coronary artery disease majority agreement was 82%; in patients having a three-vessel disease majority agreement was also higher with 100% compared with those patients having only a one-vessel or two-vessel disease.

In the light of these observation we think that the full potential of this technique will be achieved when quantitative analytic methods become available.

Quantitative approaches for the analysis of regional wall motion have been attempted (65-67). These approaches require a contouring system in which the operator identifies the endocardial border in diastole and in systole and then measurements are made by computer. Therefore the operator dependence is still retained in this form of analysis.

Moreover the image quality is a limiting factor because the endocardial "dropout" in some patients.

Recently an automatic edge detection algorithm has been proposed that facilitates on-line analysis of left ventricular performance (68).

Colour Doppler imaging has been applied for the definition of the acceleration of the myocardial walls, with improvement of image quality (69). These advances may facilitate the quantification of regional function in the future.

Significant developments is also made in the sphere of backscatter analysis and tissue characterisation.

It has been showed in animal models that both the mean amplitude of ultrasonic backscatter and its cyclic variation during systole and diastole may be alterate by ischemia (70-71).

Picano (72) has recently reported that videodensitometry may be used to show that asynergic myocardium due to ischemia demonstrates increased echodensity.

The difference between the backscatter characteristics of myocardium and blood has been used to obtain automatic detection and tracking of left ventricular cavity (73). Moreover on-line quantification of left ventricular volumes has been utilized during dobutamine echocardiography (74) although no correlates with coronary anatomy or regional left ventricular function have been reported.

Finally, the development of transpulmonary contrast agents may enhance the ability to localize the endocardium. Besides, contrast echocardiography may permit quantification of myocardial perfusion. In the future it will be possible to evaluate both perfusion and function using ultrasound techniques at both rest and stress.

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